Boehringer Ingelheim

Clinical Overview

	Doc. No.: U09-3815-01 **Doc. Id.:** US
Drug Substance:	Dabigatran etexilate (as mesilate)
Dosage Form, Strength:	Hard capsules, 110 mg and 150 mg
Document Title:	Clinical Overview MAA/ NDA for the prevention of stroke, non-CNS systemic embolism and reduction of vascular mortality in subjects with non-valvular atrial fibrillation.
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2.5.1 PRODUCT DEVELOPMENT RATIONALE

Target indication
The target indication is the prevention of stroke, non-CNS systemic embolism and reduction of vascular mortality in subjects with non-valvular atrial fibrillation.

Scientific background
Atrial fibrillation increases the risk of stroke and death. Most of the strokes, fatal and non-fatal, associated with atrial fibrillation are ischemic in nature, usually a result of a thromboembolism with the origin in a left atrial thrombus.

Dabigatran etexilate is an orally available prodrug of dabigatran, a competitive, reversible direct thrombin inhibitor. Dabigatran inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. The inhibition of the thrombin dependent conversion of fibrinogen to fibrin prevents formation of thrombus. Given its key role in thrombotic events, thrombin inhibition represents a therapeutic target for numerous thromboembolic diseases. Direct thrombin inhibitors are proven antithrombotics, in acute coronary syndromes (e.g. hirudin), in venous thrombosis and in subjects with atrial fibrillation (e.g. ximelagatran).

The data in this application demonstrate that the high dose of dabigatran is superior to warfarin in reducing a composite of stroke and systemic embolii, life-threatening bleeds, hemorrhagic strokes and vascular mortality, with higher rates of MI and GI hemorrhage than warfarin. The low dose of dabigatran is non-inferior to warfarin in reducing a composite of stroke and systemic embolii but with a lower rate of hemorrhagic stroke, other life-threatening bleeding, major bleeding and and total bleeding, with a higher rates of MI and GI hemorrhage. Other than bleeding, only gastrointestinal events have been identified as adverse drug reactions during clinical trials or in animal studies. These data support the registration of Pradaxa to prevent stroke and systemic emboli in subjects with atrial fibrillation.

National Scientific Advice has been given by France and Sweden in April 2005. Scientific advice on the design of the Phase III program has been given by FDA in July 2005. The minutes of this FDA meeting are available in Module 1.6.3.

2.5.1.1 CLINICAL DEVELOPMENT

Phase I studies established the initial safety profile of dabigatran etexilate in healthy volunteers and optimised the formulation. Tests of anticoagulant activity in Phase I subjects (aPTT, ECT, TT and INR) helped predict the dose range likely to be effective in humans. A series of multiple Phase I studies examined the drug-drug and drug-food interaction potential of dabigatran etexilate. These drug interaction studies established that there were no interactions based on cytochrome P-450 metabolism, that strong P-glycoprotein inhibitors could increase the concentrations of dabigatran in plasma, but that concomitant use of proton pump inhibitors decreased dabigatran concentrations.

Dose finding of dabigatran etexilate in patients was first conducted in orthopedic surgery subjects at high risk for venous thromboembolism (VTE). A placebo-controlled study in

Japan in subjects undergoing total knee replacement, demonstrated that treatment with dabigatran etexilate was significantly more effective than placebo in the prevention of venous thromboembolism (1160.50 [U07-3436-01]). A dose range of 100 to 300 mg per day for 5-10 days was identified as the likely range for efficacy and safety in that indication (1160.19 [U04-1195-01]). This initial Phase II data established that the primary metabolite of dabigatran etexilate, dabigatran, was an active antithrombotic agent and likely to have clinical utility in the treatment of thromboembolic disorders. Nine Phase III trials are ongoing or have been completed and have a total target enrollment of over 37,000 patients. In addition, an 1800 subject trial in patients with acute coronary syndrome has recently been completed.

Dabigatran has been registered in several countries, including the European Union, for the prevention of venous thromboembolic events in patients undergoing major orthopedic surgery.

Subjects with AF have an increased risk of stroke and death. Warfarin and other Vitamin K antagonists reduce the risk of both stroke and death in this population but increase the risk of bleeding (Hart 1999, [P99-02978]). In addition to the bleeding risks, warfarin must be regularly monitored and has multiple food and drug interactions which complicate its use. Many subjects treated with warfarin are either inadequately treated or discontinue therapy (Connolly 2008, [R08-5518]). Thus, there is a need for a new anticoagulant that is safe, effective and easy to use.

A 12 week Phase II trial in atrial fibrillation subjects at moderate to high risk of stroke explored the safety and efficacy of dabigatran etexilate at doses of 50, 150 or 300 mg twice daily, with or without aspirin, compared to warfarin alone (INR of 2-3; PETRO, 1160.20 [U06-1615-02]). This study, and the bleeding data from a rollover study in these subjects (PETRO-EX, 1160.42 [U09-3247-01]) established the maximal tolerated dose of dabigatran to be less than 300 mg BID. These studies also established that the minimal effective dose for prevention of stroke and SEE was greater than 150 mg/day (Figure 2.5.1.1: 1). In parallel, a small Phase II study in Japanese AF subjects compared 110 mg BID, 150 mg BID, and warfarin titrated to an INR 2-3 (1160.49 [U07-3126]). This study supported the safety of these two doses in subjects with atrial fibrillation.

The Phase II data identified a possible dose range (greater than 150 mg/day and less than 600 mg/day) that might prove to be safe and effective compared to warfarin.

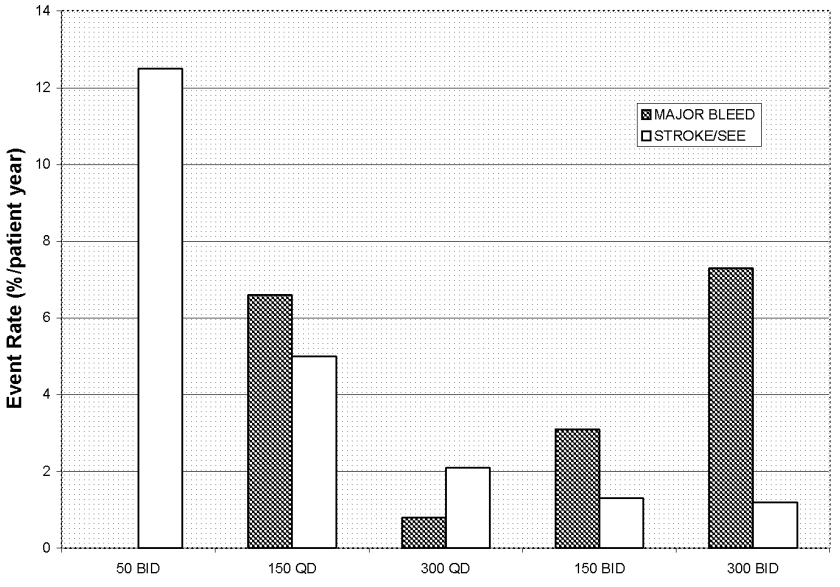


Figure 2.5.1.1: 1 Major Bleed and Stroke/SEE rates, combined data from PETRO (1160.20) and PETRO-EX (1160.42), by dose group.

Source data: 1160.42 [U09-3247-01, Table 11.4.1.2: 1 and Table 12.2.2.1: 1]

2.5.1.2 STUDY DESIGN AND METHODOLOGY

2.5.1.2.1 Phase III critical design aspects

Given the need for a new oral anticoagulant (see Section 2.5.1.1), the decision to conduct a large, single, Phase III non-inferiority trial versus warfarin was driven by two considerations. First, warfarin, or other Vitamin K antagonists, are the standard of care for subjects with AF at moderate to high risk of stroke. A comparison against placebo in this indication was not ethical. Therefore, comparison against an active control group required a non-inferiority design since there was no expectation that superiority over a very effective drug could be achieved. The second consideration for a single large trial was the low rate of primary events in this population. An event rate of 1.5-2.5% per year, a conservative non-inferiority margin, and sufficient power, required a trial size of at least 5,000 subjects per group for a comparison of a single dose of dabigatran with warfarin. This was larger than any previous single trial ever conducted in subjects with atrial fibrillation and larger than the combined Phase III trials of another direct thrombin inhibitor, ximelagatran, also recently tested in this indication.

2.5 CLINICAL OVERVIEW

In the RE-LY study, the protocol specified non-inferiority margin (NIM) for the hazard ratio was 1.46. The NIM was based on the risk reduction observed for warfarin in 6 historical placebo-controlled trials, 62% (95% CI 48-72%) reduction in the risk of preventing stroke in subjects with non-valvular atrial fibrillation in warfarin-treated subjects compared to placebo-treated subjects (Hart 1999 [P99-02978]). The NIM preserved 50% of the benefit of warfarin therapy based on the lower bound of the 95% confidence interval of the VKA effect, 48%. The analysis of the primary endpoint in RE-LY compared the upper bound of the 95% confidence interval of the hazard ratio for each dabigatran dose compared to warfarin, to assess whether the individual dabigatran doses met the protocol pre-specified NIM, 1.46. To adjust for multiple testing, the Hochberg procedure was used. With the assumption of an annual stroke rate of 1.6%, a 2 year recruitment and 1 year follow-up period, approximately 5000 subjects per group would be required to assess non-inferiority with 84% power at an alpha of 0.025 (450 primary events).

Due to rapid enrollment, the enrollment was projected to complete 5-6 months early. Because of the uncertainties of overall event rate and the duration of follow-up required, the Operations Committee of RELY decided in mid-2007 to continue recruitment until the middle of December 2007 with a minimum 1 year follow-up of the last patient. It was estimated that 3,000 additional patients could be recruited in this time in addition to the original planned 15,000 patients. This approach protected against the possibility that the actual annual event rate would decrease as the trial progressed, as occurred in ACTIVE-W. The anticipated increase of patient numbers would either increase the number of primary events over the original target, thus increasing power, or counterbalance any decrease in event rate which might occur over the remaining duration of the trial. With 18,000 subjects (6,000 per group), the power was 90%.

The choice of an open-label design was based on several considerations. Most important was that treatment with dabigatran was fundamentally different from treatment with warfarin. Warfarin, and other VKAs, require regular monitoring and dose adjustments. Proper use of warfarin also requires careful attention to diet and concomitant medication use because of their drug-food and drug-drug interactions. Dabigatran, on the other hand, required no monitoring, no dose adjustments, no dietary restrictions and had a very limited list of potential drug interactions. In addition, because of the different pharmacokinetics of the two drugs, interruption of treatment for surgery or procedures is also different. In most subjects, dabigatran can be stopped 24 h before a procedure and re-started without bridging, whereas warfarin requires 3-5 days interruption before a procedure, often with bridging therapy to deal with the additional 3-5 days to get back to therapeutic levels. These differences in the management of treatments would be obscured by a double-blind design and it would not be possible to ascertain their relevance in the population to be treated.

An open-label Phase III trial, with appropriate measures to minimize bias, is more likely than a double-blind trial to represent the individual advantages and disadvantages of each therapy. In an open-label study, the primary safety and efficacy endpoints need to be clinically relevant, objective, and not subject to bias. Stroke/SEE and major bleeding are clinically relevant and objective endpoints. Blinded adjudication of these endpoints and all other clinically relevant outcomes minimizes bias. The PROBE design (**p**rospective, **r**andomized,

open trial with **b**linded adjudication of **e**vents) was therefore selected as the design for the Phase III trial.

The PROBE design has the advantages of being able to compare therapies which may be quite different but cannot remove all the bias of an open-label design, especially in the areas of treatment discontinuation and adverse event reporting, where the biases of the investigator and the subject may come into play. Several added measures to protect against bias were therefore incorporated into the trial (see Section 2.5.1.2.2).

Another previous approach included two Phase III trials, one open-label and one double-blind [(SPORTIF III), R03-2719; (SPORTIF V), P05-01352]. However, the stroke rates of the control groups differed by a factor of almost 2, suggesting that the open-label design may have influenced the event rates on warfarin (the rates on ximelagatran were the same in both trials). Recent analyses have shown that the differences in the warfarin event rates between the two trials could be accounted for by differences in the demographics, the level of INR control, and the use of concomitant aspirin use (Hylek et al.,[R08-1726]).

Including two doses in Phase III had several advantages. The Phase II data identified a dose range based on bleeding and the occurrence of thromboembolic events but did not have sufficient precision to unequivocally identify the optimal dose. Comparing two different doses to warfarin yielded more information for dosing recommendations. This doubles the amount of safety data available for the test compound compared to a single dose. The two blinded doses increased the strength of a single trial by providing two separate, blinded, and independent comparisons of test treatment against warfarin.

2.5.1.2.2 The Methodology of RE-LY

As a single, open-label, non-inferiority trial, it was important that the study conduct be rigorous in order to ensure reliable and interpretable results. The following aspects of the methodology helped to assure the integrity of the study and provide a high level of confidence in the validity of the results.

Large, Multicenter, Multinational: 18,113 subjects were randomized in the RE-LY study at 951 sites in 44 countries. The international nature of the trial ensures applicability of the results across many regions. The large treatment effects can be detected with high precision and reliability while modest effects can also be detected with reasonable accuracy. The size of the trial also permits evaluation of important subgroups.

Completeness of Data Collection: In a non-inferiority trial, rigorous data collection helps ensure that a lack of treatment difference is not due to poor follow-up of subjects. In RE-LY, 99.6% of subjects were followed for outcomes or vital status for the entire duration of the trial. Of 18,113 subjects randomized, 42 subjects (0.2%) were lost to follow up and 128 subjects (0.7%) withdrew consent.

Replication: Testing two blinded doses provides confirmatory data. Consistency of response or dose response across blinded treatments provides additional assurance of drug effect.

Endpoint Adjudication and Sources of Bias: All study endpoints were blindly adjudicated. The endpoints in this population were clinically relevant and objective (e.g. stroke, death, MI, major bleeding), thus mitigating the role of bias. In addition, several measures were undertaken to minimize other sources of bias, including ascertainment bias in detection of important clinical events. These have been summarized in [Module 5.3.5.3]. Compliance or ascertainment bias could change the frequency of these adjudicated outcomes, but compliance measurements (e.g., INR control with warfarin) can assess the role of this effect.

Blindness to Treatment Effects: The organisational structure of the study and its overall conduct was designed to ensure that neither sponsor nor anyone else involved in the conduct of the study except the Data Safety and Monitoring Board (DSMB) had access to aggregated, "by treatment" oucome data, unblinded safety data (other than expedited safety reports forwarded to regulators and investigators) or any "by treatment" data analyses until after database lock. To assure this, the study database was independently managed and analysed by Population Health Research Institute (PHRI) in Hamilton Ontario. Processes within PHRI ensured blinding of all participants to "by treatment" analyses were reviewed by an independent auditor. The goals and outcome of this audit are in [Module 5.3.5.3]. An Operations Committee led by the co-principal investigators and co-chairmen and the sponsor, with other representatives from Uppsala Research Centre, Lankenau Medical Research Institute and Boehringer-Ingelheim was responsible for study design, performance and oversight, scientific integrity and reporting. The Operations Committee was assisted by an international Steering Committee of country national coordinators.

Summary: The implementation of extensive measures minimized bias in the collection and assessment of study data and prevented the sponsor, the academic collaborators and PHRI from knowledge of treatment effects during the course of the study. These measures, together with study size and design, provide assurance of robust, reliable, and credible results.

2.5.1.2.3 RE-LY—Implications of the Non-Inferiority Study Design

The purpose of this section is to examine the underlying assumptions of a non-inferiority trial and determine whether they are fulfilled in the RE-LY trial (1160.26 [U09-3249-01]). The assumptions focus on three topics: reliable estimates of efficacy of the reference treatment, ensuring the estimates of the reference treatment apply to the current trial setting, and conducting the trial with rigor.

Essential Elements

The evidence for efficacy in a non-inferiority trial depends on the similarity of outcomes between a test treatment and a standard treatment, not the differences between e.g., test treatment and placebo. The specification of this similarity is done by establishing that the test treatment is not worse than standard treatment (non-inferior) by a, prespecified amount. Inherent in this calculation is that the test treatment is superior to placebo. To do this, important assumptions must be fulfilled:

1. *The standard treatment has clinical efficacy of substantial magnitude that is precisely estimated, ideally using data from multiple adequate and well-controlled trials, with such estimates being relevant to the setting of the non-inferiority trial.*

2. *The non-inferiority design must be implemented in a rigorous manner to ensure that reliable and interpretable evidence is provided.*

(Fleming, [R08-1363], and Koch, [P08-03495])

The RE-LY trial was evaluated to determine whether it fulfilled each component of these requirements.

Element 1: Warfarin as Effective Standard Treatment

In RE-LY, the standard treatment is full dose warfarin, titrated to a target INR of 2-3. The efficacy of full dose warfarin for prevention of stroke in subjects with atrial fibrillation has been demonstrated in 6 placebo-controlled trials. These 6 historical trials were reported from 1989 to 1992 and a meta-analysis has shown that the overall risk reduction versus placebo in the prevention of stroke was 62% (95% CI 48-72%); (Hart et al 1999 [P99-02978]). Clearly this almost 2/3 reduction in strokes is both of "substantial magnitude" and "precisely estimated", with a lower bound of the 95%CI at nearly 50% reduction in relative risk versus placebo. These six trials represent a total subject exposure of 4599 subject-years (Jackson et al [R08-2662]). All trials were randomized and had an appropriate control group.

There is some variability in the designs of the 6 placebo-controlled trials:

- Some subjects used VKAs other than warfarin but the drugs have the same mechanism of action and are titrated to the same pharmacodynamic effect.
- Four of the 6 trials were open-label and 2 double-blind, with no appreciable difference in the risk reduction.
- The target INR was variable, ranging from a low of 1.4 to a high of 4.5 (estimated based on prothrombin times).
- Most of the trials were stopped early, which may tend to overestimate the effect size. On the other hand, the early stop also resulted in widened confidence intervals around the effect size compared to completely recruited trials, making required sample sizes larger. The non-inferiority comparison in RE-LY was based on an effect size that may have been overestimated but with a wider confidence interval. These effects go in opposite directions and tend to cancel each other out.

Thus, the requirement for standard treatment to demonstrate efficacy of substantial magnitude that is precisely estimated and is based on multiple trials, appears to be fulfilled.

Element 2: Constancy—The Estimate of Efficacy Applies to the Current Setting

Briefly, constancy requires that the estimate of efficacy of standard treatment from the previous placebo-controlled trials must also be a reasonable estimate of its effect in the

setting of the (current) non-inferiority trial. If there was a placebo group in our trial, the effect size of warfarin vs. placebo should be the same as that observed from the historical trials. A diminished effect size of standard treatment would make it easier for the test treatment to appear effective.

To examine constancy, it is reasonable to look at two groups of factors:

- the subject population in the current trial and ways in which it might differ from the original trial
- any recent evidence that either the endpoint of interest (stroke and systemic embolism) is diminished in the population under study or that warfarin effects are diminished in current practice because of differences in patient care

The patient population in the historical trials differed in several respects from the current non-inferiority trial.

There was a large proportion of 'low risk' subjects in the historical trials. Low risk subjects are excluded in the current setting. The reason for exclusion of low risk subjects is that the same historical trials that form the basis for the efficacy estimate of warfarin demonstrated that such subjects had minimal benefit from warfarin. Warfarin's historical effect on stroke was seen primarily in the moderate to high risk groups. Resultant clinical guidelines recommend use of warfarin only in moderate to high risk subjects with AF. However, this difference from historical trials works in favour of magnifying the warfarin effect in the current setting—exclusion of low risk subjects from the current setting will tend to increase the efficacy of warfarin compared to historical trials. Even if the constancy assumption did not hold, the error would be in favor of warfarin in RE-LY.

The current setting limited the trial population to those with one or more risk factors (age≥75 years, heart failure, previous stroke or SEE, age >65 years with one of coronary disease, diabetes mellitus, or hypertension). The demographics of the historical trials were not identical to the current setting but these concomitant diagnoses were present to a greater or lesser extent in the various trials (Atrial Fibrillation Investigators meta-analysis, [P05-06213]). The demographics do not appear to be qualitatively different from previous trials.

Subjects in the historical AF trials were limited largely to those diagnosed with permanent or persistent AF, while the current setting also allows entry of subjects with paroxysmal AF. If the latter subgroup of AF subjects have lower stroke rates than the other types of AF, this might lead to an overestimation of the efficacy of warfarin in the current setting. Non-inferiority to warfarin in this setting might be concluded when both are equally ineffective. However, the risk of stroke in subjects with paroxysmal AF is similar to the risk in subjects with persistent or permanent AF (Hohnloser, [P07-14830]). In RE-LY there was no appreciable difference in the primary endpoint rate on warfarin among the three categories of AF (1.74%, 1.76%, and 1.60 %/year for paroxysmal, persistent, and permanent AF, respectively). This factor does not perturb the constancy assumption.

The historical warfarin trials entered almost exclusively subjects who had not been previously exposed to warfarin. Recent literature suggests that these subjects may have higher risk of bleeds and strokes compared to a population who has been receiving chronic treatment (Hylek, [P07-07848]). Fifty percent of subjects recruited into the current RE-LY trial were previous users of warfarin or other VKAs. If the rates of stroke were lower in this subgroup, it would tend to underestimate the efficacy of warfarin compared to historical trials. In fact, in RE-LY there were no large differences across these subgroups, indicating that this factor did not affect the constancy assumption.

Medication use varies widely between trials from the early 1990s and the current setting. Notably the use of statins, use of antihypertensives may lead to an overall decrease in the rate of stroke among AF subjects. Effective treatment of hypertension will lower systolic pressure and may directly affect the rate of hemorrhagic stroke. Concomitant medications may have led to a lower event rate in modern trials.

If the endpoint of interest were diminished in the current population, it could have the effect of making warfarin or a test treatment appear more effective in lowering the absolute rates of stroke than they actually were. However, since the basis for the non-inferiority estimate in RE-LY is a relative risk calculation, the absolute rates are less likely to impact the conclusion of non-inferiority than if we used a fixed margin for non-inferiority.

There is good evidence from recent epidemiological studies that untreated AF results in high rates of stroke (Singer, [R09-4831]), thus indicating that the endpoint is still present in the population under study. Estimated annual incidence of stroke in the non-treated AF population ranges from 2-5% per year in moderate risk subjects to 5-10% per year in high risk subjects (ACC/AHA/ESC AF Guideline, [P06-08196]). Despite changes in medication and demographics, the current setting still allows for studying the effect of the standard treatment on the incidence of stroke/SEE.

The effect of warfarin might have diminished over time. In the current setting, this would have the effect of comparing dabigatran etexilate to a standard treatment that is less effective than in the original trials. One could conclude that dabigatran is as effective as an agent which may not have preserved the effects from the original trials. In that case, the constancy assumption would be violated. In fact, there have been several recent trials which have demonstrated that the stroke rate in subjects treated with warfarin is either superior to an alternative treatment (ACTIVE-W, [P06-06455]), or poor control of INR in warfarin-treated subjects is associated with increased rates of stroke (SPORTIF III and V, [R03-2719, P05-01352], AFFIRM, [R09-1282], ACTIVE-W, [P06-06455]). Thus, there is ample evidence from recent trials that warfarin is effective in the prevention of stroke, and that the rigor of INR control is directly related to its effectiveness.

Estimates relative to the setting of the NI trial

Ischemic stroke is still occurring at high rates in untreated subjects (Singer, [R09-4831]). In addition, warfarin was shown to be active in recent trials ($p<0.05$ in ACTIVE-W, low event rates in SPORTIF and AMADEUS). The demographics of recent trials and a registry indicate subjects have multiple risk factors for stroke, with very few low risk subjects

(Go, [R03-1232], Jackson et al., [R08-2662]). Thus, recent use of warfarin in AF suggest that warfarin is an active control agent and the population included is at moderate to high risk of stroke.

Element 3: Implementation of Non-Inferiority Design in a Rigorous Manner

In a trial design that is focused on showing similarity, poor conduct and data collection will blur the distinction between treatments and increase the chances of success.

Dropout rates: In RE-LY, treatment discontinuation occurred at the rate of approximately 10% per year for the dabigatran treatment arms and ~7.5%/year on warfarin. However, subjects continued to be followed in the trial. At trial closeout, 15 Dec 2008 to 15 March 2009, vital status was obtained on all but 42 subjects lost-to follow-up and 128 subjects who had withdrawn consent. Thus >99 % of subjects were followed up. This rigor in follow-up mitigates against unidentified differences in treatment that might cast doubt on a non-inferiority analysis.

Compliance and INR control: The compliance to dabigatran, as determined by capsule counts was at least 95%. Compliance was defined as taking 80-120% of the capsules. Assessment of compliance in the control group, warfarin, was established based on INR control. Overall time in therapeutic range was 64% overall, which is similar to other recent trials with warfarin in AF subjects. In addition, both bleeding and efficacy outcomes on warfarin were sensitive to INR control, substantiating that warfarin is active.

Open label: The open label design for warfarin compared to dabigatran is subject to potential bias in reporting of adverse events and in discontinuation rates. In fact, discontinuation rates were ~5% greater on dabigatran treatment. The intention-to-treat analysis of RE-LY included the subjects off-treatment. The greater discontinuation rates would tend to dilute any effect of dabigatran compared to warfarin. Despite over 75% of subjects reporting adverse events, only gastrointestinal events occurred with more frequency on dabigatran.

Measures to control bias: A summary of measures to control bias is given in [Module 5.3.5.3]. Clearly objective, clinically relevant endpoints, blinded adjudication of efficacy and safety endpoints, blinding of the dabigatran doses, symptom questionnaires for stroke and bleeding, screening of hospitalizations and adverse events for possible outcomes are some of the measures used to ensure accurate and valid data collection.

Site Monitoring: All sites were monitored regularly for protocol and GCP compliance, including drug accountability, reporting of outcomes and adverse events, subject safety and responsibilities of the investigator.

These measures ensured that trial conduct was rigorous and that the reporting of major outcome events and adverse events was thorough and accurate.

Conclusion

The appropriateness of the active control, warfarin, and its behavior as an active treatment in the setting of the current trial have been demonstrated. The rigor of RE-LY has been shown

by almost complete patient follow up with high medication adherence, as well as dose response and consistent results across subgroups. The rigor has ensured that the results are interpretable and reflect the attributes of the treatments.

2.5.1.2.4 Summary of RE-LY Results

Design

RE-LY was a Phase III, prospective, randomized, open-label, multinational (44 countries) trial of stroke prevention in subjects with nonvalvular atrial fibrillation (AF) and at least one risk factor for stroke. A total of 18,113 subjects were randomized to one of two blinded doses of dabigatran etexilate (110 mg BID or 150 mg BID, designated DE110 BID and DE150 BID) or to warfarin, titrated to a target INR of 2 to 3. The subject population included balanced proportions of Vitamin K antagonist (VKA) naïve and VKA-experienced subjects. The primary outcome was stroke (including hemorrhagic) and non-CNS systemic embolism (SEE). A secondary outcome was a composite of stroke, SEE and all cause death. Safety outcomes included bleeding, liver function abnormalities, and other adverse events.

The trial database was located at Population Health Research Institute (PHRI), McMaster University, Hamilton Canada. The study conduct was managed by lead academics from McMaster University, Lankenau Institute in Philadelphia, Pennsylvania, Uppsala Clinical Research Institute in Uppsala Sweden, and the sponsor. Study sites were initiated and monitored by the sponsor. A blinded adjudication committee adjudicated all cases of death, stroke, SE, major bleeding, myocardial infarction, pulmonary embolism, and transient ischemic attack (TIA). The safety of the subjects during the trial conduct was managed through a Data and Safety Monitoring Board who met periodically to review the data for safety and efficacy. The design was previously published (Ezekowitz, [P09-05487]). The trial was conducted according to GCP.

During the trial, five protocol amendments were enacted. Amendment 1 mandated balanced randomization of VKA-naïve and experienced subjects at each site. Amendment 2 increased the target recruitment to 18,000 subjects. Amendment 3 was a decrease in schedule of LFT monitoring. Amendment 4 contraindicated quinidine. Amendment 5 included amended recommendations for mangement of subjects during surgery, initiated a thrombin time substudy, and gave guidance for study closeout.

In the RE-LY study, the protocol specified non-inferiority margin (NIM) for the hazard ratio was 1.46, based on the meta-analysis of 6 placebo-controlled studies (62% reduction, 95% CI 48-72%). The NIM preserved 50% of the benefit of warfarin therapy based on the lower bound of the 95% confidence interval of the VKA effect compared to placebo, 48%. The primary analysis compared the upper bound of the 95% confidence interval of the hazard ratio for each dabigatran dose compared to warfarin to assess whether the individual dabigatran doses met the protocol pre-specified NIM, 1.46, using the Hochberg procedure to adjust for multiple testing.

2.5 CLINICAL OVERVIEW

Demographics and Exposure

Subject enrollment began on Dec 22, 2005 and concluded on Dec 15, 2007. Follow-up continued for 1 year after the last subject in, and the final follow-up visits started on Dec15 2008 and completed on Mar 15 2009. There were 18,113 subjects enrolled. Median duration of the study was 24 months. Median duration of exposure to treatment was 22.1 months overall, with over 10,000 subject-years of exposure per treatment group. Treatment groups were well balanced for baseline characteristics. Subjects were elderly subjects (mean age 71.5 years), 63.6% male, 70% Caucasian, with an even mix of paroxysmal, persistent, and permanent AF. By study definition 49.6% were VKA-experienced (at least 61 days of VKA use ever). Baseline aspirin use occurred in ~40% of subjects. The mean CHADS2 score was 2.1. Prior stroke occurred in 12.5% of subjects and approximately 32% had heart failure.

The mean time in therapeutic range (INR 2.0 to 3.0) for all subjects on warfarin was 64.2% (median 67.1%). The time in therapeutic range was greater for VKA-experienced subjects than for VKA naïve subjects (mean 66.9% vs. 61.6%, median 69.2% vs. 64.6%) with most of this difference occurring primarily in the first 6-9 months of VKA treatment in this study. Permanent discontinuation of study medication during the trial was greater in the two dabigatran treatment groups (22.4% and 23.1% for DE110 BID and DE150 BID, respectively) compared to warfarin, 18.1%.

Primary Efficacy Outcome

Stroke or systemic embolism occurred in 182 subjects on DE110 BID (1.53%/year), 133 subjects on DE150 BID (1.10%/year) and 198 subjects on warfarin (1.68%/year). The test for non-inferiority to warfarin was significant for both doses of dabigatran ($p< 0.0001$). The high dose of dabigatran was superior to warfarin in the reduction of stroke or systemic embolism (RR 0.66, 95%CI 0.53-0.82, $p< 0.001$). A sensitivity analysis designed to test non-inferiority and superiority of dabigatran doses compared to warfarin using the first 450 outcome events confirmed the results from the primary analysis. Non-inferiority was achieved for both dabigatran doses, $p< 0.0001$, and DE150 BID was superior to warfarin (RR 0.71, 95%CI: 0.56-0.90, $p=0.0043$).

Safety-Bleeding

Major bleeding occurred in 318 subjects on DE110 BID (2.67%/year), 375 on DE150 BID (3.11%/year) and 396 on warfarin (3.36%/year). DE110 BID led to a 21% reduction in major bleeding compared to warfarin (DE110 BID, RR 0.79, 95%CI: 0.68-0.92, $p=0.002$) while there was no significant difference in major bleeding between DE150 BID and warfarin (DE150, RR 0.93, 95%CI 0.81-1.07, $p=0.32$). Hemorrhagic stroke occurred in 14 subjects on DE110 (0.12%/year), 12 subjects on DE150 (0.10%/year) and 45 subjects on warfarin (0.38%/year). Both doses of dabigatran led to statistically significant reductions in hemorrhagic stroke compared to warfarin (DE110, RR 0.31, 95%CI 0.17-0.56, $p<0.001$; DE150, RR 0.26, 95%CI 0.14-0.49, $p<0.001$) In addition, both doses of dabigatran resulted in a reduction in all bleeding (major +minor) compared to warfarin (RR for DE110 vs. warfarin 0.79, 95%CI 0.74-0.84, $p< 0.0001$; RR for DE150 vs warfarin 0.91, 95%CI 0.86-0.97,

p< 0.0029). The lower dabigatran dose led to significantly less bleeding than the higher dabigatran dose (DE110 vs. DE150, RR 0.86, 95%CI 0.81-0.92, p< 0.0001).

Other Safety

Dyspepsia occurred in ~6% of dabigatran-treated subjects compared to 1.4% in warfarin-treated subjects.

Liver function abnormalities were closely monitored during the trial. LFTs were monitored monthly in every subject during the first year of exposure and 4 monthly thereafter. Transaminases, alkaline phosphatase or bilirubin elevations >2x ULN (upper limit of normal) prompted an alert status, where subjects were followed more closely. For elevations of >3x ULN, the additional monitoring was intensified. Concomitant transaminase elevations >3xULN and bilirubin elevations >2xULN, or transaminases >5x ULN, prompted immediate discontinuation of treatment and rigorous follow-up for a clinical cause. After approximately 10,000 subjects had been recruited and over 6,000 subjects had been treated for at least 6 months, a pre-specified interim analysis of hepatic safety was performed by the Data Monitoring Committee. There was no indication of hepatotoxicity. This led to a decrease in the frequency of monitoring during the first year of expsoure for all subjects.

At the end of the trial, there was no evidence of any increased incidence of transaminase elevations, or concomitant transaminase and bilirubin elevations, in the dabigatran treated subjects compared to warfarin treated subjects throughout the trial. For transaminases >3xULN, there were 121 subjects (2.0%) on DE110, 111 subjects (1.8%) on DE150 and 126 subjects (2.1%) on warfarin. For potential Hy's Law cases, there were 11 subjects (0.2%) on DE110 BID, 14 subjects (0.2%) on DE150 BID and 22 subjects (0.4%) on warfarin.

The increased rate of discontinuation of dabigatran compared to warfarin was accounted for by the following reasons: subject did not want to take study drug, serious adverse event, outcome event (ischemic stroke, SEE, MI), and minor bleeds.

Outcomes

There were 4,069 outcomes (deaths, strokes, non-CNS systemic emboli, pulmonary emboli, TIAs, myocardial infarctions and major bleeds) which were blindly adjudicated. At least two adjudicators reviewed each event and if there was disagreement, additional adjudicators reviewed the case. Overall, there was a high concordance between the site and the adjudication (91.1%). Notable differences occurred in adjudication of SEEs, where the adjudicators rejected almost half of the events (N= 92 reported, 49% agreement), and in adjudication of uncertain strokes, many of which were reclassified by the adjudication process to hemorrhagic or ischemic (N=78 reported, 23.1% agreement). In addition, 14 strokes were identified in the process of adjudicating the TIAs.

The efficacy and safety data are consistent and demonstrate a clear risk-benefit advantage of dabigatran compared to warfarin. There are important reductions in hemorrhagic stroke and intracranial hemorrhage (ICH) with both doses of dabigatran compared to warfarin. ICH, including subdural and subarachnoid bleeds in addition to intracerebral bleeds, was reduced 59% and 71% compared to warfarin (for DE110, RR 0.29, 95%CI: 0.19-0.45, p< 0.001; for

DE150, RR 0.41, 95%CI: 0.28-0.61, p< 0.001). The high dose of dabigatran reduces ischemic stroke compared to warfarin . The effect of dabigatran on stroke is similar for both disabling stroke and for mild stroke, with better efficacy of the dabigatran high dose compared to warfarin. There is also a decrease of 12% in all cause mortality and in vascular death (16%) with the high dose of dabigatran compared to warfarin. Death occurred in 487 subjects on warfarin (4.13% per year), 445 (3.74% per year) on DE110 BID (RR 0.90, 95%CI: 0.79-1.03; p=0.12), and 437 (3.63% per year) on DE150 BID (RR 0.88, 95% CI: 0.77-1.00; p=0.0475).

For the outcome of pulmonary embolism, the absolute frequency is low and similar across all treatment groups (DE110 BID: 0.12%/year, DE150 BID: 0.15%/year, warfarin: 0.09%/year). While the overall frequency of myocardial infarction, is low, there is a higher rate of MI in subjects treated with dabigatran, both dose groups, compared to warfarin. The effect appears to be independent of dose although the numbers are small. Myocardial infarction occurred in 63 subjects on warfarin (0.53 % per year) in 86 subjects on DE110 BID (0.72% per year) (RR 1.35, 95% CI: 0.96-1.87; p=0.08), and in 89 subjects on DE150 BID (0.74 % per year) (RR 1.38, 95% CI: 1.00-1.91; p=0.049).

For the secondary endpoint of stroke/SEE/death the rates were DE110 BID 4.83%, DE150 BID 4.30%, and warfarin 5.17%. The DE110 BID dose was similar to warfarin (RR 0.93, 95%CI: 0.83-1.05, p=0.2337) but the high dose was superior to warfarin (RR 0.83, 95%CI: 0.74-0.93, p=0.0016) and different from D110 D110 vs. D150 (RR 1.13, 95%CI: 1.00-1.27, p=0.0491).

For the pre-specified composite endpoint for risk benefit (stroke/SEE/PE/MI/death/major bleed) dabigatran 150 mg BID is superior to warfarin. The annualized rates were 7.08%/year for DE110, 6.89%/year for DE150 and 7.63%/year for warfarin (DE110 vs warfarin RR 0.92, 95%CI: 0.84-1.02, p=0.1003; DE150 vs warfarin (RR 0.90, 95%CI: 0.82-1.00, p=0.0372).

The RE-LY trial establishes the safety and efficacy of dabigatran etexilate in prevention of stroke in subjects with non-valvular atrial fibrillation (AF) and at least one risk factor for stroke.

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Dabigatran etexilate mesilate has low solubility and high intrinsic passive permeability characteristics *in vitro*. The solubility of the compound was shown to be significantly pH dependent with increased solubility at acidic pH, and limited solubility at alkaline pH values [Pharmaceutical Development of Dabigatran Etexilate Capsules, Module 3.2.P.2]. Active ingredient layered pellets including a tartaric acid core as a solubilizer filled into hard capsules were developed as the final clinical trial and commercial dosage form. This formulation was used as final dose form in the Phase II and III trials in subjects with atrial fibrillation.

The absolute bioavailability after oral administration is approximately 3% to 7% (1160.05 [U01-1807]). Plasma concentrations are linearly related to dose over the range 10 mg to 400 mg single dose and 50 to 400 mg tid. A second generation drug product, not used in Phase III clinical trials, was found to be bioequivalent to the first generation drug product using an average, scaled, bioequivalence approach, (1160.70 [U09-1051-01]).

The prodrug dabigatran etexilate is rapidly absorbed and converted by esterase-catalysed hydrolysis to dabigatran. Dabigatran median t_{max} values are observed at about 1.5 and 2.0 hours, indicating rapid absorption and conversion of dabigatran etexilate to the active moiety dabigatran. Conversion of the prodrug dabigatran etexilate occurs via two intermediates, BIBR 951 (an active thrombin inhibitor) and BIBR 1087 (pharmacologically inactive). Across the dose ranges investigated, the pro-drug and the two intermediates are generally observed at low concentrations close to the detection limits and for short periods of time (< 6 h) after dabigatran etexilate administration (1160.60 [U06-1614-01], 1160.51 [U06-1705-01]). Non-specific plasma- and liver-esterases are responsible for the hydrolysis of dabigatran etexilate in humans. There is no involvement of cytochrome P450 isoenzymes in the prodrug conversion and dabigatran metabolism, (A170/04LU,B2476 [U05-1339]).

After multiple dosing the between-subject variability ranged between 33.0 and 57.7% gCV and 31.4 and 53.5% for $C_{max,ss}$ and $AUC_{\tau,ss}$, respectively [1160.57 [U06-1610]; 1160.58 [U06-1611]; 1160.59 [U06-1612]; 1160.90 [U09-3246-01]. In a Phase II clinical study, subjects who received 150 mg BID for up to 4 years showed an intra-individual variability in trough concentrations of approximately 39%.

There was a small increase in bioavailability with food. A high fat, high caloric breakfast, delayed the time to peak from 2 to 4 hours post-dose, increased the average C_{max} and $AUC_{0-\infty}$ values of dabigatran by about 9% and 27%, relative to the fasted state with the 150 mg HPMC capsule (1160.40 [U04-1459-01]). The inter-subject variability (%gCV) of the $AUC_{0-\infty}$ in the fasted state was 51% compared to 32% in the fed state, suggesting a reduced variability in the total extent of absorption. Based on these findings, dabigatran etexilate HPMC capsules can be taken with or without food. If the capsule is opened and the pellets swallowed separately, the bioavailability is increased by 75-85%. Therefore the capsule should not be opened (1160.87 [U09-1839-01]).

Low gastric acidity decreases the bioavailability of dabigatran etexilate 20-25%. Pantoprazole, a proton pump inhibitor, was co-administered with dabigatran etexilate

(1160.10 [U03-1878]). The average bioavailability relative to the reference treatment without pantoprazole on day 7 was 79.6% (CI 66.7% – 94.8%).

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

The effects of dabigatran etexilate have been investigated in 40 Phase I studies, 6 completed Phase II studies in AF subjects and subjects undergoing orthopedic surgery, and 4 completed Phase III studies. Over 10,000 subjects/subjects have been included in completed studies in the primary VTE prevention indication. Almost 700 subjects have been included in completed Phase II SPAF studies and over 18,000 in the Phase III study in AF subjects, RE-LY.

This clinical pharmacology overview will focus on the following PK and PD topics:

- The influence of age, gender, race, impaired hepatic and renal function on dabigatran pharmacokinetics
- The potential for pharmacokinetic or pharmacodynamic interactions with concomitant administration of drugs
- The pharmacokinetics and pharmacodynamics in orthopaedic surgery subjects and subjects with non valvular atrial fibrillation
- The exposure-response relationship for efficacy and safety in the target subject population

2.5.3.1 PHARMACOKINETICS

After a single oral dose of dabigatran etexilate, the pharmacokinetic profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations, with C_{max} attained within 0.5 and 2.0 hours post administration. After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal elimination half-life of 9.4 h and 10.1 h in young male and female subjects, respectively, and 10.7 h and 11.2 h in healthy elderly (≥ 65 years) male and female volunteers, respectively (1160_meta-analysis-PK-01 [U09-1363-02], Table 7.2.2: 1). The half-life is prolonged to 15.3 h and 18.4 h in patients with mild or moderate renal impairment, respectively (1160.23 [U06-1704]). The half-life was independent of dose. Cmax and the area under the plasma concentration-time curve increased in proportion with dose. (Figure 2.5.3.1: 1)

After repeated dosing, steady state was reached by Day 3 of treatment [1160.10, U03-1878]. The average ratios of accumulation observed with 150 mg dabigatran etexilate twice daily were 1.4- and 1.3-fold for AUC and C_{max}, respectively (1160.29 [U06-3091]).

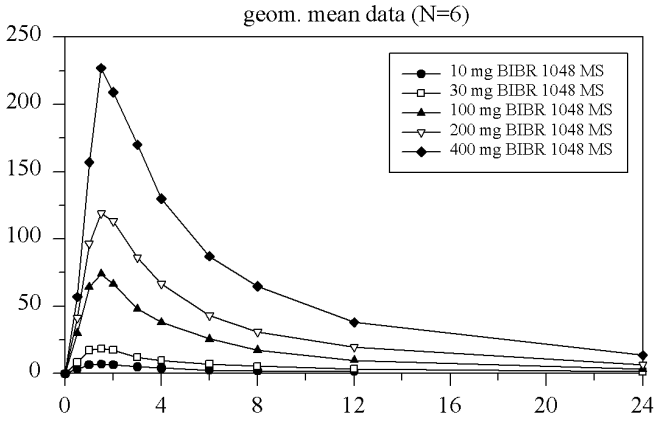


Figure 2.5.3.1: 1 Geometric mean plot of plasma concentration of dabigatran versus time. Single oral administration of 10, 30, 100, 200 and 400 mg dabigatran etexilate (BIBR 1048 MS) as solution

Source data: 1160.1 [U99-1502]

2.5.3.2 PHARMACODYNAMICS

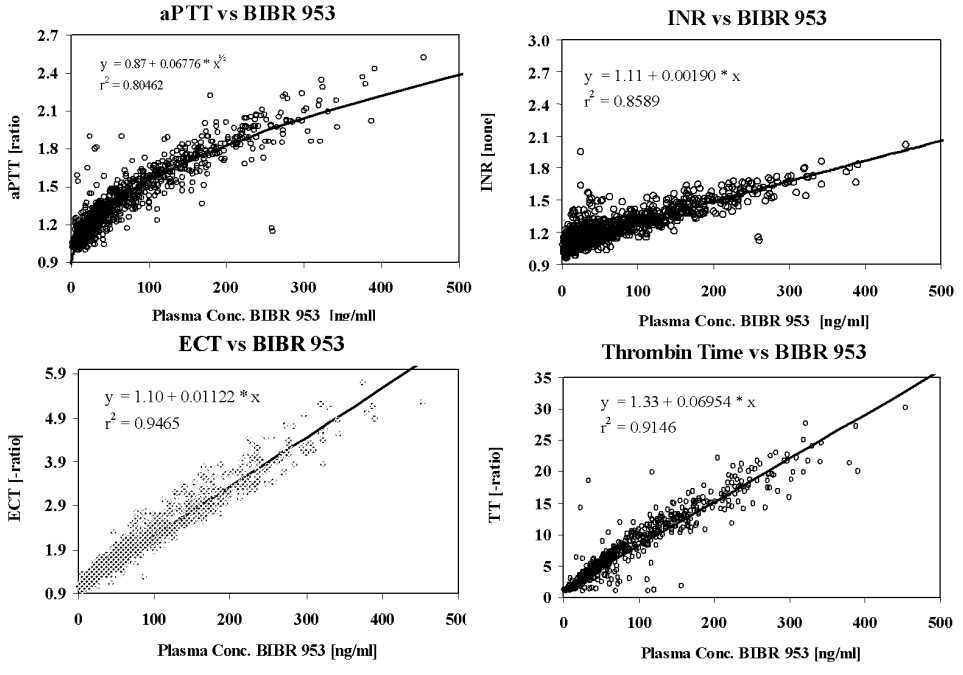


Figure 2.5.3.2: 1 Relationship between aPTT, INR, ECT and TT and dabigatran (BIBR 953) plasma concentration

Source Data: 1160.14 [U00-1855]

A comparison of dabigatran plasma concentrations and the corresponding aPTT prolongation (left top panel), INR (right top panel), ECT (bottom left panel), and TT (bottom right panel) in healthy volunteers are shown in Figure 2.5.3.2: 1. Changes in aPTT correlate non-linearly with dabigatran concentrations. INR is linearly correlated with dabigatran concentrations but has poor sensitivity to dabigatran concentrations in the therapeutic range. ECT is highly correlated with dabigatran concentrations, has low variability but is not widely available in hospital laboratories. Thrombin time is highly correlated with dabigatran concentrations and has low variability. However, the wide variation in methods of measuring thrombin time and the standards used may limit its use as a monitoring tool. The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test maybe useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity.

2.5.3.3 INTRINSIC FACTORS

Due to the predominant urinary excretion of dabigatran, renal function is the most important single factor influencing the pharmacokinetics of dabigatran. Other intrinsic factors such as age and gender/sex were also found to contribute to the inter-individual variability in CL [U09-1399-02]. Old age had an additional effect upon dabigatran exposure which is not related to the normal age associated decline in renal function in the elderly (U09-1399-02). Body weight, race or moderate hepatic impairment were shown not to be covariates leading to a meaningful deviation in PK.

2.5.3.3.1 Effect of renal insufficiency

In a Phase I study, subjects with moderate renal impairment (CrCL 30 - < 50 mL/min) had dabigatran plasma levels 3.15 higher than subjects with normal renal function (> 80 mL/min). In AF patients in RE-LY, the differences in concentrations between these two classes of renal function was 2.3-fold. The median CrCl in RE-LY was 68.4 mL/min. Almost half (45.8%) of the RE-LY subjects had a CrCl ≥50-80 mL/min. The dabigatran plasma levels in these subjects were 1.56-fold higher than subjects with moderate renal impairment (1160.26 [U09-3249-01].

In subjects with severe renal impairment (CrCL < 30 mL/min), the mean AUC of dabigatran is increased 6.3 fold compared to normal renal function. The gMean half-lives were 15.3, 18.4, and 27.2 hours in mild, moderate and severe renal impairment, respectively. Additionally, dabigatran concentration measurements in dialysis fluid from subjects undergoing maintenance dialysis indicate that dabigatran is dialyzable with 61 to 68% of systemic dabigatran being removed by dialysis (1160.23 [U06-1704]).

2.5.3.3.2 Effect of liver insufficiency

The influence of hepatic impairment on the absorption and bioconversion of dabigatran etexilate was assessed in subjects with moderate hepatic impairment (1160.51 [U06-1705-01]). The mean AUCs and half-lives for dabigatran were similar to healthy controls. The bioconversion of the prodrug to dabigatran was slightly slower in subjects with moderate hepatic impairment. Accordingly, the AUCs of dabigatran etexilate (BIBR 1048)

and the two intermediates, BIBR 1087 and BIBR 951, were increased several fold. Protein binding and the extent of glucuronidation were not affected in subjects with moderate hepatic impairment.

2.5.3.3.3 Effect of gender, age and weight

A meta-analysis on data from Phase I and Phase II studies revealed a gender effect with female subjects having a generally higher exposure than males after the same dose of dabigatran etexilate, approximately 31-46%. This is consistent with RE-LY (30% increase in trough and post-dose concentrations in females) but the effect was not associated with any increase in bleeding rate. The effect is most likely caused by the on average 29.5% lower CrCL in female subjects. From the final model built on data from orthopedic surgery (BISTRO II, Phase II) and AF subjects (PETRO, Phase II) female gender was associated with a 12.5% lower CL/F compared with males [U09-1399-02].

Age effects on the the PK of dabigatran paralleled the effect of age on renal function. Half-life increased from 9-10 hours in healthy young volunteers to 10.7 h and 11.2 h in healthy elderly (≥ 65 years) male and female volunteers, (1160_meta-analysis-PK-01 [U09-1363-02]). However, the pooled PopPK analysis showed age was an additional factor independent of renal function. There was a decline in individual CL/F by 0.66% for each year increase from 68 years of age (1160.42 [U09-3247-01]). The effect of age was confirmed in the RE-LY study. Compared with patients aged between 65 and 75 years, patients ≥ 75 years had a ~31% higher trough concentration and subjects < 65 years had a ~ 22% lower trough level (1160.26 [U09-3249-01]). These observations indicate that age related differences in exposure are largely related to renal function, though there is a smaller additional effect of age itself.

Based on the pooled PopPK, weight affected volume of distribution (V2/F). A change in 1 kg body weight changes V2/F by 1.10%. The effect on exposure is, however, only minor. No effect of weight or BMI on bleeding was seen in RE-LY. As observed for gender effects, it is likely that any detectable difference in low versus high body weight patients is largely attributed to body-weight-related differences in renal function (1160_meta-analysis-PK-01 [U09-1363-02], Table 7.1: 7).

2.5.3.3.4 Effect of different ethnic origin

PK and resulting exposure were not meaningfully different in healthy subjects as well as in subjects of Caucasian or Japanese origin (PK0747E [U07-3471]). Race was also not found to be a significant covariate in the PopPK analysis on pooled data from healthy volunteers, OS- and AF subjects (1160.42 [U09-3247-01]). The Phase III subgroup analyses in subjects with AF (RE-LY) confirmed the lack of any meaningful differences in the PK of dabigatran between Asian, Caucasian and Black subjects.

2.5.3.3.5 Pharmacogenetics

No relation between the PK exposure parameters C_{max} or AUC and *MDR1* genotype became apparent. The *MDR1*-genotype did, thus, not contribute to the intersubject variability in dabigatran PK (1160_meta-analysis-PK-01 [U09-1363-02]).

2.5.3.4 EXTRINSIC FACTORS

Dabigatran, the pro-drug, dabigatran etexilate, and the two intermediate metabolites, BIBR 951 BS and BIBR 1087 SE, are not substrates and do not inhibit or induce any cytochrome P450 (CYP) isoenzymes in any preclinical test systems.

Dabigatran etexilate but not the active moiety, dabigatran, is a substrate of the efflux transporter P-glycoprotein (P-gp). Accordingly, the bioavailability of dabigatran is increased when potent P-gp inhibitors like verapamil, quinidine, amiodarone or ketoconazole are co-administered. The interaction seems to be limited to effects on intestinal absorption. Rifampicin, an inducer of P-gp reduced the bioavailability of free and total dabigatran by approximately 66%.

2.5.3.4.1 CYP 450 Isoenzymes

Three studies were performed in healthy volunteers to elucidate the effect of three common co-medications: atorvastatin (3A4 substrate), diclofenac (2C9 substrate, substrate of glucuronosyltransferases 1A1 and 1A3) and amiodarone (2C9, 2D6 and 3A4 inhibitor). Atorvastatin (1160.58 [U06-1611]) and diclofenac (1160.7 [U06-1608]) did not alter the pharmacokinetics and pharmacodynamics of dabigatran nor did dabigatran exert a relevant effect on those drugs.

Amiodarone on the other hand clearly increased the bioavailability of dabigatran etexilate, an effect which can be attributed to the P-gp inhibition by amiodarone (see below).

2.5.3.4.2 P-glycoprotein inhibitors

A series of *in vivo* drug interaction studies, designed to detect maximum effects, was performed in healthy volunteers using the following P-gp inhibitors or substrates: amiodarone (presumed moderate to potent inhibitor of P-gp; additional inhibitor of 2C9, 2D6 and 3A), clarithromycin (presumed potent P-gp inhibitor), verapamil (presumed potent P-gp inhibitor), quinidine (presumed potent P-gp inhibitor), ketoconazole (potent inhibitor of P-gp and CYP3A), rifampicin (inducer of P-gp and various Phase I and II enzymes like CYP3A, CYP2C, UGT) and digoxin (P-glycoprotein substrate). Most of these probe drugs were chosen based on their *in vitro* potency to inhibit the p-gp enyzme and their frequency of use in the target indication ([U05-2159], [U07-3036], [U07-3354]).

Dabigatran AUC and C_{max} were increased by about 60% and 50%, respectively in the presence of a single oral dose of 600 mg amiodarone (1160.57 [U06-1610]). In the RE-LY study the trough concentrations increased by 13% in 1309 patients taking amiodarone, with no detectable increase in bleeding.

The maximum effect after multiple dosing of clarithromycin at a dose of 500 mg bid was a 15% to 20% increase in $AUC_{0-\infty}$ and C_{max} of dabigatran (1160.82 [U08-2188-01]).

The effects of the P-gp probe inhibitor verapamil were evaluated after single and multiple dose administration of 120 mg verapamil immediate release (IR) and/or 240 mg verapamil extended release (ER) formulations to healthy volunteers. In addition, different timing of the inhibitor related to dabigatran etexilate (1 h before, concurrently and 2 h after) was assessed. The most prominent effect on dabigatran bioavailability was observed when dabigatran etexilate was given 1 h after a single dose of 120 mg verapamil IR. $AUC_{0-\infty}$ and C_{max} were increased on average by ~145% to ~180% (2.45-2.8-fold) respectively. The effect was clearly diminished when a single oral dose of 240 mg verapamil ER was given together with dabigatran etexilate (~70-90% increase in $AUC_{0-\infty}$ and C_{max}). After three days of dosing with twice daily verapamil, the elevations in these dabigatran parameters were diminished further to an increase of 54% and 63% compared to control (1160.74 [U09-1052-01]).

In the RE-LY study, verapamil was co-administered with dabigatran in 632 patients. Dabigatran trough and peak, $C_{pre,ss}$ and $C_{2,ss}$, were elevated on average by 16% and 20%, respectively. There was no consistent evidence of bleeding in patients concomitantly taking verapamil.

Two Phase I studies on quinidine effects were conducted. Trial 1160.75 [U08-3299-01] was terminated prematurely due to intolerability of a single dose of 600 mg quinidine, specifically hypotension, syncope, nausea and vomiting. An inter-individual comparison was possible for only 3 subjects who had received dabigatran etexilate after quinidine to those (N = 9) who had only received dabigatran etexilate the results indicated that quinidine approximately doubled the C_{max} and AUC of dabigatran. The results of this study led to a contraindication of quinidine co-medication in the EU-label and, moreover, to corresponding amendments of ongoing clinical trials to ensure patient safety in the absence of additional data.

Therefore, to assess the role of dabigatran, if any, on the adverse effects of hypotension, syncope, nausea and vomiting in 1160.75, a second quinidine study, 1160.90, was conducted. In this trial quinidine was given as 200 mg dose every 2nd hour up to a dose of 1000 mg. Dabigatran etexilate was dosed to steady-state with or without quinidine pre-dosing. Dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 53% and 56%, respectively. No effect on the PK of dabigatran was observed when quinidine was given after dabigatran (1160.90 [U09-3246-01]). The syncope, hypotension, nausea and vomiting observed in the previous study did not occur with chronic dabigatran administration. Hypotension did occur with quinidine. This repeated exploration of the effects of quinidine, using a cumulative dose of 1000 mg qd, confirmed the previous hypothesis that the hypotensive effects observed in the first quinidine interaction study were induced by quinidine.

There were 46 patients in RE-LY who were on quinidine and dabigatran in whom we measured plasma concentrations. There was a 15% elevation when the two drugs were co-administered. There was no detectable effect on bleeding. These results of a small increase concentrations and lack of effect on bleeding are similar to what was seen with amiodarone. Based on these results BI thinks that a contraindication for the use of dabigatran etexilate in concomitant therapy with quinidine is not justified.

Co-administration of ketoconazole, a potent inhibitor of P-gp increased dabigatran AUC and C_{max} by approximately 2.5-fold after single and multiple dosing (1160.101 [U09-1350-01]).

The PK of co-administered P-gp substrates like digoxin (1160.59 [U06-1612]) or the inhibitors (clarithromycin, verapamil, quinidine, ketoconazole, amiodarone) was not affected by dabigatran etexilate confirming the *in vitro* results that neither dabigatran etexilate nor its intermediate metabolites or the active moiety dabigatran are inhibitors of P-gp.

Pre-dosing of the probe inducer rifampicin at a dose of 600 mg qd for 7 days decreased dabigatran peak and total exposure by approximately 66% (1160.100 [U09-1349-01]).

Patient data and meta-analysis

The effect of drugs that are known to inhibit P-gp on the pharmacokinetic profile of dabigatran was investigated in the pooled PopPK analysis and in the Phase III study (RE-LY) in AF subjects. In RE-LY verapamil, amiodarone, diltiazem and quinidine were assessed specifically (N= 632, 1309, 1012, and 46, respectively) as well as in the combined potent P-gp inhibitor assessment (N=2818); the latter additionally included clarithromycin, cyclosporine, nelfinavir, ketoconazole, ritonavir, saquinavir, reserpine and tacrolimus. Rifampicin and St John´s wort were assessed specifically and together with other possible P-gp inducers, i.e. amprenavir, avasimibe, tenofovir but only in the Phase III study, RE-LY.

The fractional change in bioavailability (F) as derived from the final model including the data from Phase II (PETRO) was + 15.0% with any potent P-gp inhibitor co-medication [U09-1399-02].

In RE-LY, dabigatran $C_{pre,ss}$ and $C_{2,ss}$ were elevated by 20% or less with co-administration of verapamil, amiodarone, quinidine, or all P-gp inhibitors; the change was negligible in the case of diltiazem. The number of subjects was too low for any reasonable evaluation of P-gp inducers.

The general discrepancy between the results of Phase I trials, showing a clear effect by verapamil or amiodarone and the clinical data in subjects may be caused by several factors:

- continuous use of the P-gp inhibitor reducing the inhibitory effect,
- different (later) administration of the inhibitor related to dabigatran etexilate,
- dilution of the effect due to the use of lower doses of the P-gp inhibitor,
- differences in the study designs, with Phase I designed to show a maximal effect.

In summary, these data support the hypothesis that only when there are high concentrations of a strong P-gp efflux inhibitor in the gut at the time of ingestion of dabigatran etexilate, a clinically meaningful increase in the bioavailability of dabigatran etexilate is expected, resulting in higher AUC and C_{max} of the active moiety, dabigatran. Though Phase II and III data in AF subjects qualitatively confirm the results of the dedicated DDI studies using verapamil or amiodarone, the magnitude of the effect seems diminished in the target subject population and no clear correlation to the clinical response (i.e., major bleeding events) was found, especially in comparison to the combination of dabigatran with verapamil, amiodarone or diltiazem (RE-LY, 1160.26 [U09-3249-01], Table 15.3.2.2.3: 3). The number of subjects

on ketoconazole, cyclosoprine A, nelfinavir or saquinavir in the Phase III study, RE-LY was too low to draw any final conclusion on the effect of these drugs on the incidence of major or any bleeding events (RE-LY, 1160.26 [U09-3249-01], Table 15.3.2.2.3: 6 and 7),

2.5.3.4.3 Effect of drugs increasing the gastric pH

In the Phase III study, RE-LY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11%). Accordingly, PPI co-medication was not associated with a higher incidence of stroke or SEE, especially in comparison with warfarin plus PPIs. Hence, the reduced bioavailability by pantoprazole co-administration seemed to be of no clinical relevance (RE-LY, 1160.26 [U09-3249-01], Table 11.4.1.4.1: 4).

2.5.3.4.4 Pharmacodynamic Interaction

Interaction with acetylsalicylic acid (ASA): In the Phase II study in non-rheumatic AF, dabigatran etexilate was tested alone or in combination with ASA. The incidence of any bleeding was increased after ASA co-administration subjects (PETRO, 1160.20 [U06-1615-02]). No specific Phase I pharmacokinetic interaction was performed. However, PK and PD interaction with clopidogrel was investigated in a Phase I study testing the effects of a loading dose as well as the maintenance dose of clopidogrel on dabigatran exposure, and vice versa (1160.83 [U09-1547-01]). No PK or PD interaction was demonstrated. Only after a loading dose of 300 or 600 mg clopidogrel were the plasma levels of dabigatran increased by 30-40%.

Based on the large Phase III study (RE-LY, 1160.26) ASA or clopidogrel co-medication with dabigatran etexilate at dosages of 110 or 150 mg bid approximately doubled the risk of major bleeding. The same magnitude of effect of ASA or clopidogrel co-medication on bleeding was also observed for warfarin (RE-LY, 1160.26 [U09-3249-01], Tables 12.2.2.7: 1 and 15.3.2.2.3: 3). The concurrent use of parenteral antithrombotics was associated with a higher incidence of major bleeding events (RE-LY, 1160.26 [U09-3249-01], Table 15.3.2.2.3: 3). The number of subjects in RE-LY with any other specific oral antithrombotic therapy (dipyridamole, Aggrenox®, ticlopidine) was too low to draw any definitive conclusion.

In summary, the ASA and clopidogrel co-medication increase the risk of bleeding when given together with dabigatran or warfarin. Caution is warranted if combining dabigatran with ASA, clopidogrel or other platelet aggregation inhibitors. Enoxaparin pre-treatment does not affect dabigatran pharmacokinetics and dabigatran-related pharmacodynamics. A switch from enoxaparin to dabigatran etexilate is feasible without any wash-out in between.

2.5.3.4.5 Exposure-Response in AF Subjects

With twice daily oral administration of dabigatran etexilate, the plasma concentrations of total dabigatran at steady state were dose proportional between 110 mg and 150 mg doses. The geometric mean trough plasma concentrations of DE 110 and DE 150 were 64.6 ng/mL and 90.9 ng/mL, respectively. There was a significant overlap in the concentrations achieved with the two doses (Figure 2.5.3.4.5: 1). However, the differences in the doses were clinically relevant, based on the differences in efficacy and safety outcomes between the two doses.

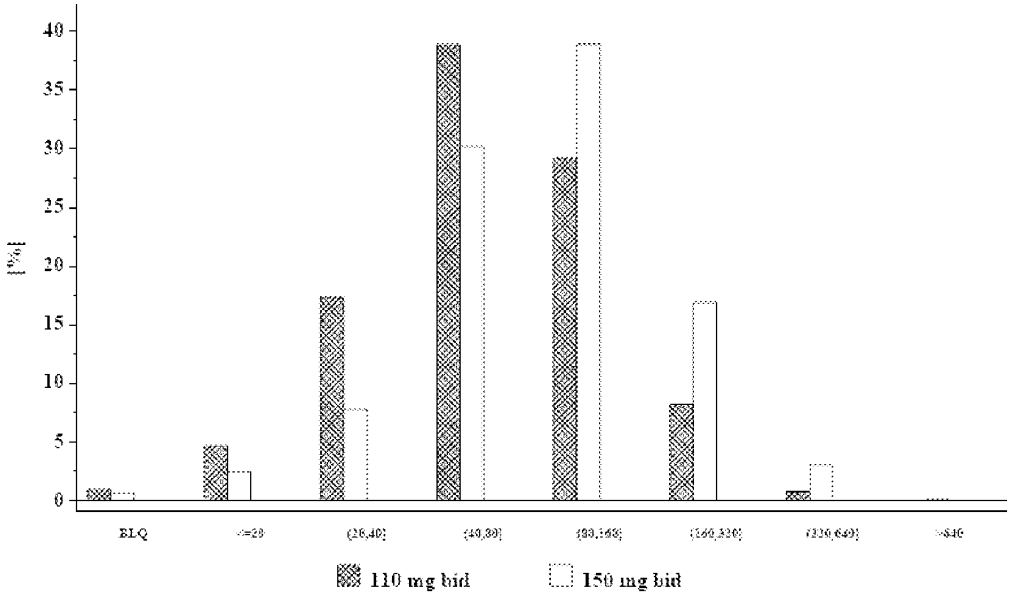
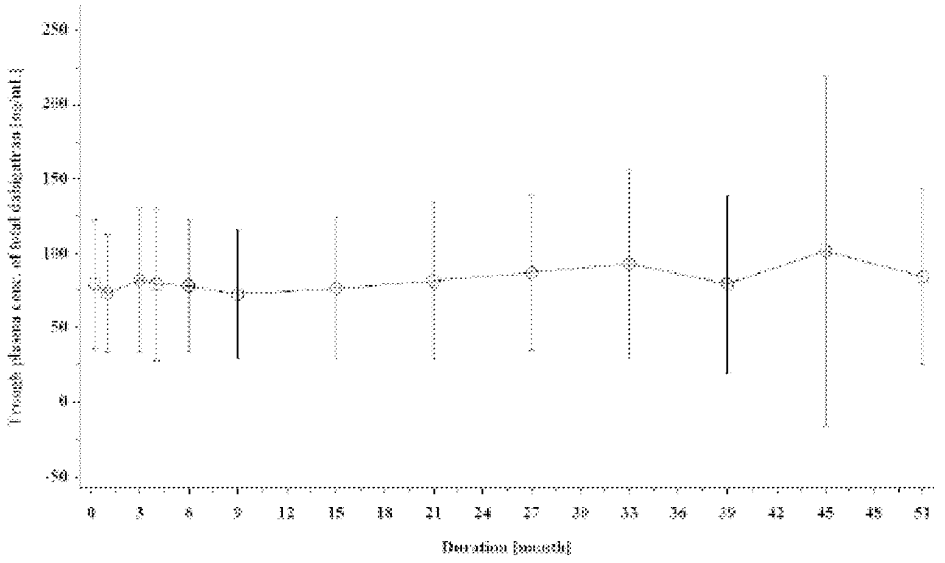


Figure 2.5.3.4.5: 1 Distribution of trough plasma concentrations for DE110 and DE 150. The X-axis categorizes plasma concentrations in ng/mL

Source data: 1160.26 [U09-3249-01] Appendix 16.1.9.5, Listing 1.5, 1.6, 1.13 and 1.14

Intra-individual Variability

During long-term treatment (12 to 51 months) with 150 mg bid dabigatran etexilate, the trough concentrations within subjects had an intra-individual variability of ~39%. For any given subject, more than 80% of the trough concentrations were within +/-30% on a log scale (Figure 2.5.3.4.5: 2). For the pharmacodynamic markers, aPTT and ECT, over 95% of the samples were within +/- 30% [1160.42; PETRO-EX study] (+/- 30% on a log scale). Chronic administraion of dabigatran etexilate is associated with acceptable within subject variability in AF patients.



40 patients who had been treated with a constant dose of 150 mg bid dabigatran etexilate for more than 3 years from the beginning of the PETRO trial.

Figure 2.5.3.4.5: 2 Arithmetic mean (+/-SD) trough plasma concentrations of total dabigatran in subjects who were treated >3 years with 150 mg bid dabigatran etexilate.

Source data: 1160.42 [U09-3247-01], Figure 11.5.2: 1

Efficacy

In the Phase III study (RE-LY, 1160.26) there was only a weak negative association between the occurrence of ischemic stroke and dabigatran trough plasma concentration. Accordingly, a logistic regression analysis did not reveal any trends in efficacy related to plasma concentrations in RE-LY (Figure 2.5.3.4.5: 3).

There was also a weak negative association between trough aPTT and the probability of stroke with a higher incidence of ischaemic stroke and SEE at shorter aPTT values (1160.26 [U09-3249-01], Figure 15.5.3: 7).

Since the dabigatran etexilate dose of 150 mg bid was significantly more efficacious than the 110 mg bid dose in RE-LY, the dose is considered to be a better predictor with respect to efficacy.

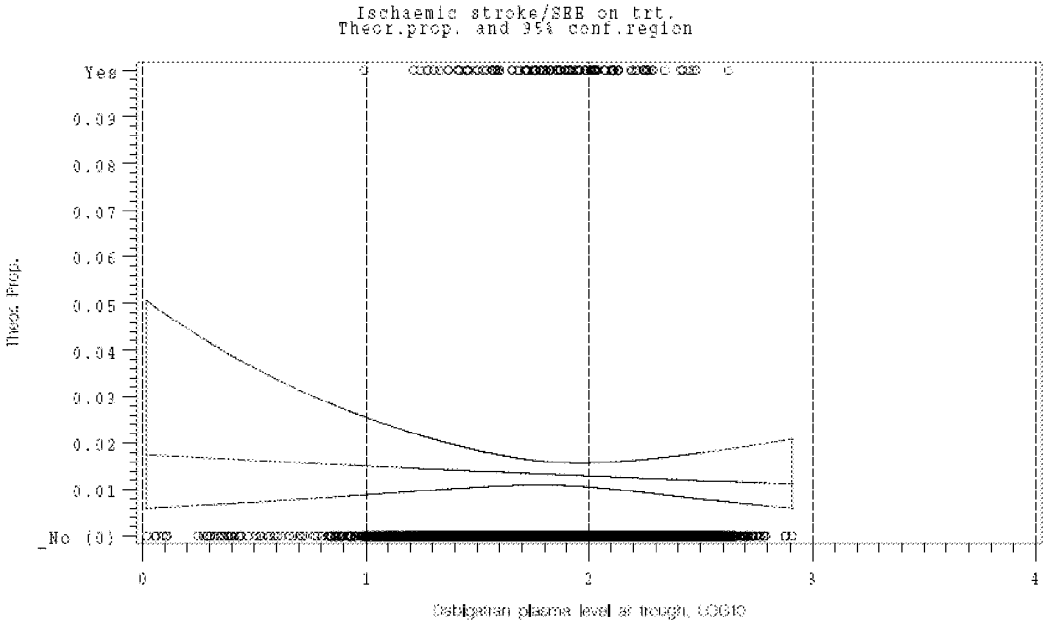


Figure 2.5.3.4.5: 3 Probability of ischaemic stroke and SEE vs. log trough plasma concentration of total dabigatran (Dabi) in AF subjects receiving either 110 or 150 mg dabigatran etexilate bid.

Source data: 1160.26 [U09-3249-01], Figure 15.5.1: 14

Safety

In RE-LY, subjects with major bleeds on dabigatran had a 57% higher geometric mean plasma concentration than subjects without bleeds (114 ng/mL vs. 72.8 ng/mL at trough). For any bleeds, there was a 19% mean increase in plasma concentrations in subjects who had any bleed compared to those with no event (86.8 ng/mL vs. 72.8 ng/mL). These findings are consistent with the increased risk of bleeding with the D 150 dose compared to D 110.

A logistic regression model correlating concentrations of total dabigatran or prolongation of aPTT and the probability of major or any bleeds was developed in all RE-LY subjects treated with dabigatran etexilate and having PK data. The trough and post-dose concentrations and aPTT changes were analysed (1160.26 [U09-3249-01], Section 15.5).

The increase of trough total dabigatran concentration was associated with increased probability of having major bleeds, as shown in Figure 2.5.3.4.5: 4, below.

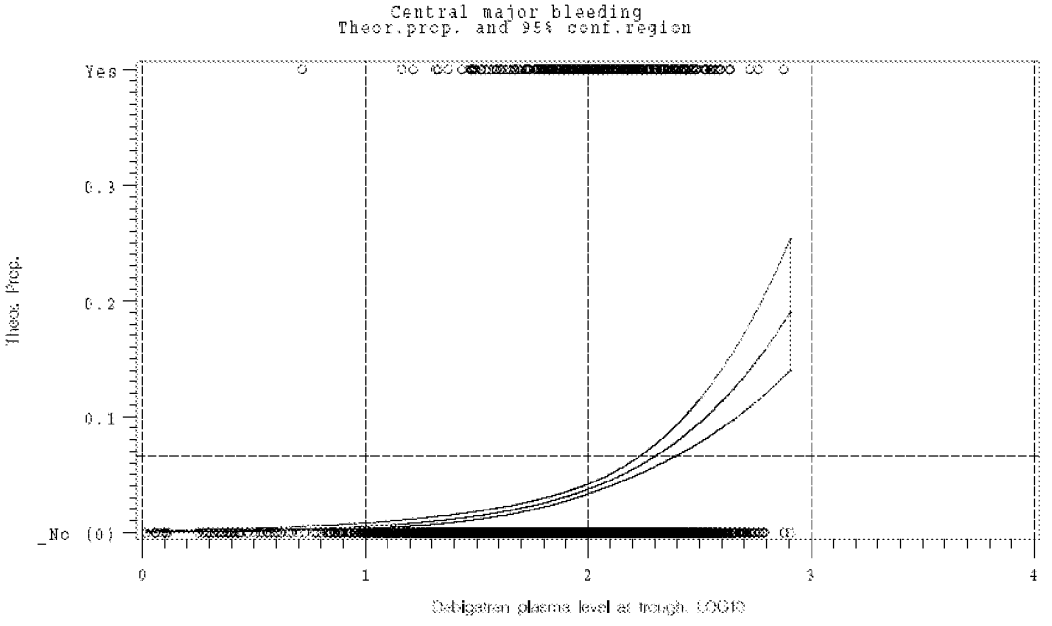


Figure 2.5.3.4.5: 4 Probability of major bleeds vs. log trough plasma concentration of total dabigatran in AF subjects receiving either 110 or 150 mg dabigatran etexilate bid.

Source data: 1160.26 [U09-3249-01], Figure 15.5.1: 1

Plasma concentrations in the subjects with hemorrhagic stroke were higher than those in the event-free subjects, despite a low incidence of hemorrhagic stroke.

Sex and age had some effect on the exposure-response relationship, with females showing a lower propensity for bleeding despite higher plasma levels while elderly (> 75 years) have higher plasma concentrations and a higher bleeding susceptibility (see additional analyses on RE-LY, 1160.26 [Module 5.3.5.3]).

The median aPTT at trough of DE 150 is 51.9 sec, with a 10^{th} percentile of 40.3 sec and a 90^{th} percentile of 76.4 sec. Trough aPTTs above 80 sec were associated with a higher major bleed rate (5.1%) than aPTTs at or below 80 sec (3.4%)

2.5.3.4.6 Clinical Pharmacology Conclusions

Plasma concentrations of total dabigatran were dose proportional between the 110 mg and 150 mg bid doses but there was a significant overlap in the plasma concentrations achieved with the two doses. Across treatments, renal function was by far the most important subject factor affecting plasma concentrations of total dabigatran. The effects of gender, age, and body weight on plasma concentrations were less strong than creatinine clearance and had no

impact on bleeding rates. Race had no obvious effect on the concentration of total dabigatran. In the Phase III trial, RE-LY, P-gp inhibitors modestly increased concentrations up to 20% but these small increases appeared not to be associated with any effect on bleeding rates. The smaller effect on concentrations in Phase III studies is in contrast to the Phase I drug interaction studies which were designed to measure maximal effects by selecting specific timepoints of drug administration and uniform fasting conditions in a carefully controlled way. These different conditions may account for the smaller effects on concentrations in Phase III.

There was no detectable association between ischemic stroke and plasma concentration of total dabigatran. Major bleeding events were associated with approximately 50% higher mean plasma concentrations. Subjects with major bleeding events also showed prolonged aPTT values. The median plasma concentration in subjects with any bleeding (minor+major) was ~20% higher (with a wide confidence interval) than in subjects who did not bleed.

2.5.4 OVERVIEW OF EFFICACY

The key evidence for efficacy of dabigatran in this indication comes from the RE-LY trial, 1160.26, with approximately 30,000 subject-years of exposure to dabigatran or warfarin and a total of 513 adjudicated primary efficacy events (1160.26 [U09-3249-01]).

Phase II trials contributed limited data for the assessment of efficacy. This is due to the fact that the incidence of the primary endpoint in stroke prevention, stroke and systemic embolic events, is in the order of 1.5-2.5% per year. With such a low event rate, Phase II trials were not of sufficient duration or sample size to record many primary efficacy events.

The 12 week dose-finding trial PETRO (1160.20 [U06-1615-02]), with 500 subjects, recorded 2 stroke/SEE events. The 12 week Phase II trial in Japan, (1160.49 [U07-3126]), recruited 174 subjects and recorded one primary event. The long-term extension of PETRO was PETRO-EX, with 361 subjects, was over 4 years duration and collected multiple primary events but this trial was uncontrolled and subjects were exposed to more than 1 dose. This data was supportive for establishing dose-response.

Consequently, this document will focus on the efficacy data from RE-LY.

2.5.4.1 DISPOSITION OF SUBJECTS

The 18,113 randomized subjects were equally distributed across the three treatment groups with 6,015 randomized to DE 110 BID, 6,076 to DE 150 BID and 6,022 to warfarin (Table 2.5.4.1: 1)

The randomization and follow-up of subjects was well executed. Randomization without subsequent treatment with at least one dose was rare (0.4% of subjects). With a median trial duration of 24 months, ~78% completed the study on medication, and all but 4% completed follow-up. Of those who did not complete follow-up, less than 1% had their vital status unknown at the end of the study. The most common reason for premature discontinuation was withdrawal of consent.

The overall treatment discontinuation rate was ~22%, with ~18% completing study follow up and 3.9% prematurely discontinuing the study. Approximately 5% more dabigatran-treated subjects discontinued treatment and completed the study, compared to warfarin treatment. The most frequent reason for permanent discontinuation of study medication was "Subject didn't want to take study drug" (7.2%). This may be related to the open label nature of the trial. Discontinuations due to subject choice, adverse events, outcome events, minor bleeds but not major bleeds, were all more common on dabigatran. Given that the overall adverse event rate was similar across treatments except for an excess of gastrointestinal events on dabigatran, it is likely that the open label nature of the trial, caution in the use of a new agent, and availability of an alternative therapy (warfarin) had an impact on discontinuation rates.

Treatment discontinuation rates in contemporary AF trials vary from ~8% to 36%, averaging ~10% per year (AMADEUS [P08-01644], ACTIVE-W [P06-06455], SPORTIF III [R03-2719] and SPORTIF V [P05-01352]).

2.5 CLINICAL OVERVIEW

Temporary treatment interruptions were common, with over 52% of subjects stopping medication at least once (Summary of Clinical Efficacy (SCE) Appendix 6). Most of the treatment interruptions were for procedures or surgery (~36%), hospitalization (~15%), adverse events (30%) and outcomes (~7%) (1160.26 [U09-3249-01], Table 15.1.1: 4). In an elderly population with multiple diseases this is not unexpected. Management of anticoagulation during treatment interruptions is important. Warfarin must generally be interrupted for 3-5 days before and after a procedure, with INR monitoring and sometimes bridging anticoagulation, whereas dabigatran could be stopped 24 hours before and restarted soon after interruption, without monitoring.

Table 2.5.4.1: 1 Disposition of subjects in Study 1160.26

	DE 110 BID N (%)	DE 150 BID N (%)	Warfarin N (%)	Total N (%)
Enrolled (screened)				20377
Not entered				2264
Entered (randomized)	6015	6076	6022	18113
Not Treated	31	17	23	71
Completed follow up	13	7	5	25
Withdrew consent or lost to follow up or other	18	10	18	46
Treated	5984 (100.0)	6059 (100.0)	5999 (100.0)	18042 (100.0)
Completed study	5775 (96.5)	5818 (96.0)	5744 (95.7)	17337 (96.1)
Completed on study medication	4593 (76.8)	4609 (76.1)	4832 (80.5)	14034 (77.8)
Completed follow up but stopped study medication prematurely*	1182 (19.8)	1209 (20.0)	912 (15.2)	3303 (18.3)
Outcome events^	417 (7.0)	427 (7.0)	330 (5.5)	1174 (6.5)
Serious AEs not related to outcome events	196 (3.3)	200 (3.3)	147 (2.5)	543 (3.0)
Subject preference	391 (6.5)	406 (6.7)	329 (5.5)	1126 (6.2)
Elevated LFT result	28 (0.5)	16 (0.3)	11 (0.2)	55 (0.3)
Hospitalisation#	142 (2.4)	154 (2.5)	156 (2.6)	452 (2.5)
Adverse Event	305 (5.1)	329 (5.4)	200 (3.3)	834 (4.6)
Other	452 (7.6)	504 (8.3)	379 (6.3)	1335 (7.4)
Premature discontinuation from study	209 (3.5)	241 (4.0)	255 (4.3)	705 (3.9)
Withdrew consent	129 (2.2)	146 (2.4)	141 (2.4)	416 (2.3)
Vital status available at study termination	82 (1.4)	98 (1.6)	108 (1.8)	288 (1.6)
No further status after consent withdrawal	47 (0.8)	48 (0.8)	33 (0.5)	128 (0.7)
Lost to follow up	17 (0.3)	33 (0.5)	39 (0.7)	89 (0.5)
Vital status available at study termination	6 (0.1)	19 (0.3)	22 (0.4)	47 (0.3)
No further status after lost to f/u	11 (0.2)	14 (0.2)	17 (0.3)	42 (0.3)
Other	63 (1.1)	62 (1.0)	75 (1.3)	200 (1.1)

* Subjects may be counted in more than one of the sub-classes
^ Outcome events include: stroke, systemic emboli, myocardial infarction, pulmonary emboli, TIA, bleed and death (1160.26 [U09-3249-01] Section 9.5.1.4)
# Hospitalization could have been for elective procedures or those not otherwise specified.
Source data: SCE Appendix 6, Table 1.2.1.1

2.5.4.2 DABIGATRAN COMPLIANCE AND INR CONTROL WITH WARFARIN

The compliance to dabigatran, as determined by capsule counts was at least 95%. Compliance was defined as taking 80-120% of the capsules. This high compliance, together with an approximate 10%/year permanent treatment discontinuation rate suggests that chronic treatment with dabigatran will result in a high proportion of subjects who will be compliant.

Compliance to warfarin was determined by INR control as assessed by the percent of time the INR was in the required target range of 2-3 (time in therapeutic range, TTR). A linear interpolation using the Rosendaal method was performed (R08-1695). The first week after randomization and warfarin interruptions or permanent discontinuation were excluded. The overall mean and median TTR were 64.2% and 67.1% [SCE Appendix 6, Table 1.2.5.13].

The INR control was variable in the trial, as expected. Variation was due to multiple factors, including previous VKA exposure, geographic region and subject and center variation.

The VKA experienced group had a higher TTR compared to the VKA naïve group throughout the study but especially during the first 6 months of treatment (Figure 2.5.4.2: 1). The overall mean and median TTR was 61.6% and 64.6%, respectively, for the VKA naïve group, and 66.9% and 69.2%, respectively, for the VKA experienced group [SCE Appendix 6, Table 1.2.5.14].

Geographically, Sweden had the highest TTR with 77% and 78% for the mean and median percent of TTR. In general, North America (US, Canada) and Western Europe had relatively better INR control than Asia and other regions The mean and median TTR was 66.7% and 68.4%, respectively, in North America and 68.7% and 71.8%, respectively, in Western Europe. The Asian region had the lowest INR control, with mean and median TTR 54.3% and 56.3%, respectively [SCE Appendix 6, Tables 1.2.5.16 and 18]. These variations may impact the rates of stroke and bleeding.

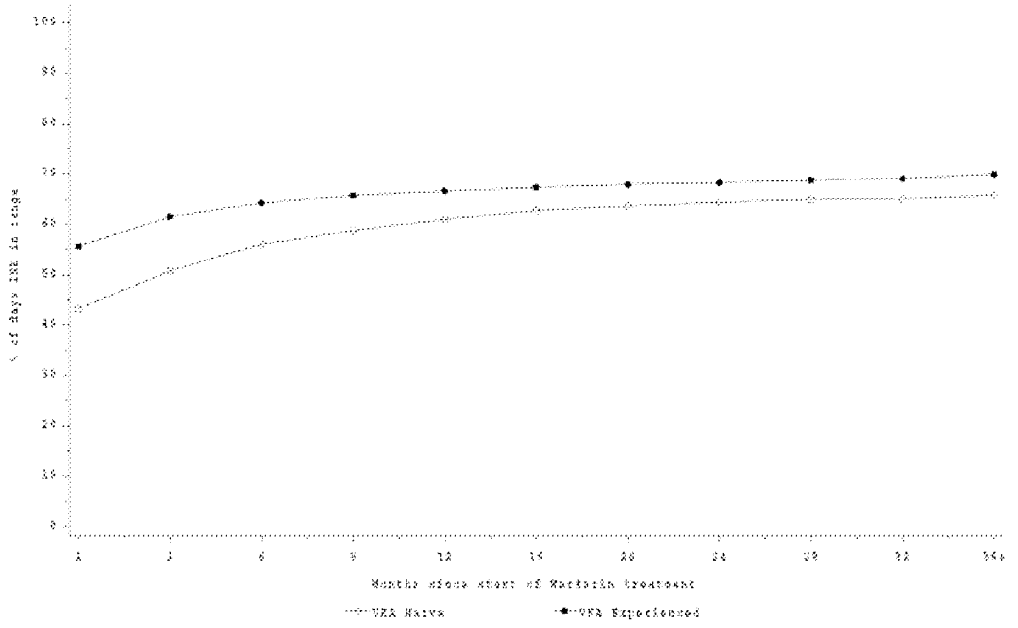


Figure 2.5.4.2: 1 Mean percentage of time of INR in range 2-3 over time by VKA status

Source data: 1160.26 [U09-3249-01] Table 15.1.5: 11, Figure 15.1.5: 5

The proportions of VKA-naïve and experienced subjects in a trial have an impact on the overall INR control (Hylek et al., [P07-07848]). This is reflected in RE-LY by the lower TTR for the VKA-naïve subjects for the first months of treatment, compared to the VKA experienced cohort.

In the historical warfarin-placebo controlled trials provided in the table below, most of the subjects were VKA-naïve (Table 2.5.4.2: 1). However, in more recent large atrial fibrillation trials, only between 15 and 27% of the subjects were not on VKA treatment at entry.

Table 2.5.4.2: 1 INR Control in historical and recent trials in subjects with atrial fibrillation.

Trial	N	INR % of Time in Therapeutic Range (TTR)	% subjects VKA-naive
Historical trials	2,854	59%	estimated ~100%
SPORTIF-V	3,922	68%	15%
SPORTIF-III	3,410	66%	27%
ACTIVE-W	6,706	64%	22%
AMADEUS	4,576	63%	24%
AFFIRM	4,060	62%	n/a

Source data: historical, [R08-2662]; SPORTIF V, [P05-01352]; SPORTIF III, [R03-2719]; ACTIVE-W, [P06-06455]; AMADEUS, [P08-01644]; AFFIRM, [R09-1282]

With the inclusion of 50% VKA-naïve subjects, the overall RE-LY INR control obtained a mean of 64.2% TTR, with poorer control in the naïve cohort compared to the experienced cohort (61.6% TTR vs. 66.9% TTR, respectively). [SCE Appendix 6, Figures 1.2.5.10 and 1.2.5.11; and Tables 1.2.5.13 and 1.2.5.14]

If the INR control in RE-LY is pro-rated to 75% for VKA-experienced subjects and 25% VKA naïve subjects, to approximate the proportions in other trials, the TTR for warfarin-randomized subjects in RE-LY would be 65.6% based on the control obtained in each cohort.

Thus the INR control obtained in RE-LY is generally representative of other large AF trials of VKA antagonists. One can conclude that the control group in this non-inferiority study represents current standard of care.

2.5.4.3 DEMOGRAPHICS: RELEVANT FEATURES

The demographics of the RE-LY study population appear in Table 2.5.4.3: 1. Concomitant diseases and selected baseline medications appear in Table 2.5.4.4: 1 and Table 2.5.4.5: 1, respectively. The subjects were demographically similar to the Phase II population and representative of the target population with atrial fibrillation who are likely to get the drug. All but 2% of subjects had at least one risk factor for stroke and the mean $CHADS_2$ score was 2.1. A brief summary of salient characteristics follows

Age As expected, this is an elderly population with mean age of 71.5 years and a high frequency of concomitant diseases (see below for concomitant diseases). There were 40% of the subjects age≥ 75 years, of whom 3,016 subjects (16.6%) were at least 80 years old at entry. Only approx. 18% are under age 65. No children were enrolled in this study (age <18). [SCE Appendix 6, Tables 3.2.23 and 1.1.1]

Ethnicity The population in RE-LY is 70% Caucasian, 16% Asian, and the remaining 14%, include 7% Hispanic/Latin and a very small proportion of black African (N~176 subjects) and other ethnicity.

Gender The subjects are primarily male, 63%, a similar proportion to other contemporary studies of AF.

Previous VKA Use The study population was balanced for Vitamin K antagonist (VKA) experience. Fifty percent of the population were VKA-naïve (<2 months lifetime exposure to a VKA), 32% with zero previous exposure and 18% with less than 2 months previous exposure. Of those with previous exposure to VKAs, over two-thirds had been treated for at least a year with only 17% treated for 2-6 months. The recruitment of a high proportion of VKA naïve subjects allowed an assessment of the impact of previous anticoagulant treatment on efficacy and safety of dabigatran and warfarin, an important consideration in starting subjects on anticoagulation (Hylek, [P07-07848], ACTIVE-W [P06-06455]).

Renal Function The median CrCl was 68.4 mL/min, lower than that for a healthy aged population. This reflects the fact that the study subjects have concomitant diseases which have adverse effects on renal function, e.g. hypertension, diabetes. The mean CrCl for a healthy 70 year old is ~ 80 ml/min (Stevens, [R09-1573]). Approximately 32% of subjects in

RE-LY have a CrCl of at least 80 mL/min. Almost 46% having a CrCl of 50-80 and 18% have CrCl between 30 and 50 mL/min.

There were 0.4% of subjects who entered the study with CrCl <30 mL/min, a protocol violation. These subjects had to achieve acceptable renal function during the study or they were withdrawn from randomized treatment.

AF Diagnosis There are approximately equal proportions of subjects with paroxysmal, persistent, or permanent atrial fibrillation. In contrast, most of the subjects in the original placebo-controlled warfarin trials in AF had persistent or permanent AF. However, even with small numbers of intermittent AF subjects (N=207) in the original trials, there was a clear effect of warfarin on stroke rates in this subgroup (AFI meta-analysis, [P05-06213]). This stroke risk of paroxysmal/intermittent AF has since been confirmed (Hohnloser, [P07-14830]). Thus, the study population is representative of the different types of AF in subjects who might be treated with an anticoagulant.

Almost half (47%) of the study population had a duration of AF of at least 2 years. Approximately 31% had newly diagnosed AF (<3 months).

Regional Recruitment Recruitment by geographic region was diverse, with strong representation from USA/Canada (~36%) and Western Europe (~26%), but also representation from regions with less experience with anticoagulation, such as Asia (~15%) and Central Europe (~12%).Thus, the data is applicable over a wide range of countries and medical practice.

In addition to the tabulated demographics, there were subjects with previous cardioversion (~27%), implanted pacemakers (10.7%), ICDs (2.2%), and previous AV ablation (~2%).

In summary, the RE-LY subjects are broadly representative of the AF population with at least one risk factor for stroke.The trial population includes a typical range of ages, both VKA naïve and experienced subjects, new onset and long standing AF, subjects with previous stroke as well as other diseases that are stroke risk factors , and a geographically diverse population.

Table 2.5.4.3: 1 Baseline demographics of RE-LY (Study 1160.26)

	DE 110mg bid	DE 150mg bid	Warfarin	Total
Randomized [N(%)]	6015 (100.0)	6076 (100.0)	6022 (100.0)	18,113 (100.0)
Age (mean, years)	71.4	71.5	71.6	71.5
Male (%)	64.3	63.2	63.3	63.6
Race: white (%)	70.0	70.2	69.8	70.0
Weight (mean, Kg)	82.9	82.4	82.6	82.6
VKA naïve (%)	50.0	49.8	51.4	50.4
Never on VKA (%)	31.1	31.4	32.7	31.7
CrCL (median, ml/min)	68.7	67.9	68.5	68.4
Systolic BP (mean, mmHg)	130.8	130.9	131.2	131.0
Diastolic BP (mean, mmHg)	77.0	77.0	77.1	77.0
AF type [N(%)]				
Persistent	1950 (32.4)	1909 (31.4)	1930 (32.0)	5789 (32.0)
Paroxysmal	1929 (32.1)	1978 (32.6)	2036 (33.8)	5943 (32.8)
Permanent	2132 (35.4)	2188 (36.0)	2055 (34.1)	6375 (35.2)
Regions [N(%)]				
USA, Canada	2166(36.0)	2200(36.2)	2167(36.0)	6533(36.1)
Central Europe	707(11.8)	706(11.6)	706(11.7)	2119(11.7)
Western Europe	1544(25.7)	1555(25.6)	1552(25.8)	4651(25.7)
Latin America	320(5.3)	320(5.3)	316(5.2)	956(5.3)
Asia	923(15.3)	933(15.4)	926(15.4)	2782(15.4)
Other	355(5.9)	362(6.0)	355(5.9)	1072(5.9)

Source data: 1160.26 [U09-3249-01]; Tables 15.1.4: 1, 3, 5, 7, and 9

2.5.4.4 CONCOMITANT DISEASES AND STROKE RISK FACTORS

Concomitant diseases in this population were primarily hypertension (79%), diabetes (~23%), coronary artery disease (~28%), and cancer (10%). There was evidence of valvular heart disease in ~22% of subjects, including 1.1% with mitral stenosis who might reasonably have been excluded from the trial under the criterion of hemodynamically relevant valve disease. Mitral regurgitation was present in 17 % of subjects. A mean systolic blood pressure of 131 mm Hg in this trial is lower than observed in recent and historical AF trials, reflecting the more aggressive use of antihypertensive drugs.

Approximately 32% of subjects had heart failure, 12.5% had a previous stroke, ~9% had a previous TIA, ~17% had a previous MI, and ~11% had a LV ejection fraction <40%. (SCE Appendix 6, Table 1.2.3.10).

The benefits of stroke prevention with anticoagulation have to be balanced against the risk of bleeding. Therefore, recent clinical guidelines require that AF subjects have at least one risk factor for stroke to be considered a candidate for anticoagulation (ACC/AHA/ESC Guideline, [P06-08196]). Table 2.5.4.4: 1 displays the risk factors required to enter the trial. While there

was an age restriction on some entry criteria (age over 65 with hypertension, diabetes or CAD), subjects under 65 with these diseases were well-represented in the trial (see above).

Different risk stratification schemes have assigned weights to several factors. Generally, previous stroke/TIA, valvular disease, and prosthetic valves are considered high risk factors, and age > 75, heart failure or reduced ejection fraction, diabetes, hypertension, and sometimes coronary artery disease are considered moderate risk factors. In RE-LY, prosthetic valves and hemodynamically relevant valvular disease were excluded but all other risk factors were well represented.

Table 2.5.4.4: 1 Baseline stroke risk factors for inclusion in the trial

	DE 110mg bid	DE 150mg bid	Warfarin	Total
	N (%)	N (%)	N (%)	N (%)
Total randomized	6015 (100.0)	6076 (100.0)	6022 (100.0)	18113 (100.0)
Stroke/SEE/TIA	1308(21.7)	1358(22.4)	1287(21.4)	3953(21.8)
LVEF <=40%	649(10.8)	652(10.7)	630(10.5)	1931(10.7)
HF (NYHA>=2)	1641(27.3)	1640(27.0)	1623(27.0)	4904(27.1)
Age>=75 years	2349(39.1)	2466(40.6)	2423(40.2)	7238(40.0)
Age>=65 years and DM	1177(19.6)	1124(18.5)	1195(19.8)	3496(19.3)
Age>=65 years and CAD	1461(24.3)	1459(24.0)	1457(24.2)	4377(24.2)
Age>=65 year & hypertension	4038(67.1)	4073(67.0)	4079(67.7)	12190(67.3)
None of the above	181(3.0)	198(3.3)	168(2.8)	547(3.0)

Source data: 1160.26 [U09-3249-01], Table 15.1.4: 13
LVEF: Left Ventricular Ejection Fraction, HF: Heart Failure; DM: Diabetes Mellitus; CAD: coronary artery disease

Stroke Risk Score: The frequency of subjects with different risks of stroke, as assessed by $CHADS_2$ score (1 point each is assigned to heart failure, hypertension, age ≥ 75, and diabetes; 2 points for previous stroke), is balanced across the range of 1, 2 and ≥3. The mean $CHADS_2$ risk score was 2.1. Thus, the study population is representative of the moderate to high risk subjects. Approximately 2.5% have $CHADS_2$ score 0, i.e. no risk factors, which is a protocol violation. This group, so called lone A Fib, is associated with lower stroke risk and guidelines recommend that they are not anticoagulated (treat with ASA only). The trial population has a similar overall level of risk in comparison to recent AF trials (ACTIVE-W SPORTIF-III), but is higher risk than AMADEUS and lower than SPORTIF V. (Table 2.5.4.4: 2)

Table 2.5.4.4: 2 Baseline $CHADS_2$ score

	DE 110mg bid	DE 150mg bid	Warfarin	Total
Total randomized [N(%)]	6015 (100.0)	6076 (100.0)	6022 (100.0)	18113 (100.0)
$CHADS_2$ score [N(%)]				
0	151 (2.5)	146 (2.4)	155 (2.6)	452 (2.5)
1	1809 (30.1)	1815 (29.9)	1707 (28.3)	5331 (29.4)
2	2088 (34.7)	2136 (35.2)	2229 (37.0)	6453 (35.6)
3+	1966 (32.7)	1979 (32.6)	1931 (32.1)	5876 (32.4)
$CHADS_2$ score				
Mean	2.1	2.1	2.1	2.1

Source data: 1160.26 [U09-3249-01], Table 15.1.4: 17

2.5.4.5 CONCOMITANT THERAPIES AT BASELINE

This population had a high frequency of concomitant therapies at baseline, as well as during the trial. For AF, treatment with either rate control or rhythm control drugs occurred and there was widespread use of diuretics, ACE inhibitors/ARBs, digoxin, calcium channel blockers, and statins. Such use is expected in a sample population with a high frequency of cardiovascular diseases.

Baseline antithrombotic use included a very high proportion of subjects on ASA (~40%) or oral anticoagulation (62%) (Table 2.5.4.5: 1). The high ASA use in RE-LY was due in part to the large proportion of VKA-naïve subjects who entered the trial with ASA as the antithrombotic of choice (54% of VKA-naïve were on ASA at baseline). In comparison, in the SPORTIF trials, 18-21% of subjects were on ASA at baseline. In ACTIVE-W, 26% of warfarin subjects were on ASA at baseline.

Table 2.5.4.5: 1 Baseline medications

	DE 110mg bid	DE 150mg bid	Warfarin	Total
Randomized	6015 (100.0)	6076 (100.0)	6022 (100.0)	18113 (100.0)
Antithrombotic Therapy				
Oral Anticoagulant	3783 (62.9)	3789 (62.4)	3708 (61.6)	11280 (62.3)
ASA	2385 (39.7)	2338 (38.5)	2431 (40.4)	7154 (39.5)
Clopidogrel	338 (5.6)	337 (5.5)	345 (5.7)	1020 (5.6)
ASA+Clopidogrel	214 (3.6)	211 (3.5)	228 (3.8)	653 (3.6)
Antihypertensive				
Diuretic	3049 (50.7)	3117 (51.3)	3073 (51.0)	9239 (51.0)
ACE inhibitor	2700 (44.9)	2755 (45.3)	2670 (44.3)	8125 (44.9)
ARB	1449 (24.1)	1470 (24.2)	1418 (23.5)	4337 (23.9)
Beta-blocker, Ca channel blocker and other drugs used in AF				
Beta-blocker	3790 (63.0)	3887 (64.0)	3722 (61.8)	11399 (62.9)
Digoxin	1781 (29.6)	1742 (28.7)	1767 (29.3)	5290 (29.2)
Amiodarone	647 (10.8)	672 (11.1)	657 (10.9)	1976 (10.9)
Verapamil	352 (5.9)	350 (5.8)	369 (6.1)	1071 (5.9)
Quinidine	28 (0.5)	25 (0.4)	31 (0.5)	84 (0.5)
Metabolic, anti-inflammatory and other				
Statin	2702 (44.9)	2682 (44.1)	2674 (44.4)	8058 (44.5)
Proton pump inhibitor	847 (14.1)	878 (14.5)	842 (14.0)	2567 (14.2)
NSAID	311 (5.2)	294 (4.8)	319 (5.3)	924 (5.1)
COX2	79 (1.3)	86 (1.4)	79 (1.3)	244 (1.3)
…Oral hypoglycemics	991 (16.5)	1009 (16.6)	995 (16.5)	2995 (16.5)
Insulin	274 (4.6)	290 (4.9)	271 (4.5)	835 (4.6)

Source data: 1160.26 [U09-3249-01] Table 15.1.4: 19

2.5.4.6 EFFICACY—PRIMARY ENDPOINT

The analysis for the primary endpoint of RELY was the time to the first occurrence of stroke/SEE. All strokes and SEEs were adjudicated. Comparisons between treatment groups for stroke/SEE were performed using a Cox regression analysis with treatment in the model.

The number of primary events, as well as the individual components and the the annualized event rates are shown in Table 2.5.4.6: 1. A total of 513 adjudicated first stroke/SEEs were observed during the trial. The Kaplan-Meier estimates are shown in Figure 2.5.4.6: 1.

Table 2.5.4.6: 1 Yearly event rate (%) for composite endpoint of stroke/SEE

	DE 110 N (%)	**DE 150 N (%)**	**Warfarin N (%)**
Subjects randomized	6015	6076	6022
Subject-years	11900	12039	11797
Subjects with stroke/SEE	182 (1.53)	133 (1.10)	198 (1.68)
Stroke	171 (1.44)	121 (1.01)	184 (1.56)
Ischemic stroke	152 (1.28)	102 (0.85)	132 (1.12)
Haemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
Stroke of uncertain classification	7 (0.06)	9 (0.07)	10 (0.08)
SEE	14 (0.12)	13 (0.11)	19 (0.16)

Each subject with an event was counted once for the composite endpoint and once for each component.
Subject-years = sum(date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100
Source data: 1160.26 [U09-3249-01]; Table 15.2.1.1: 1

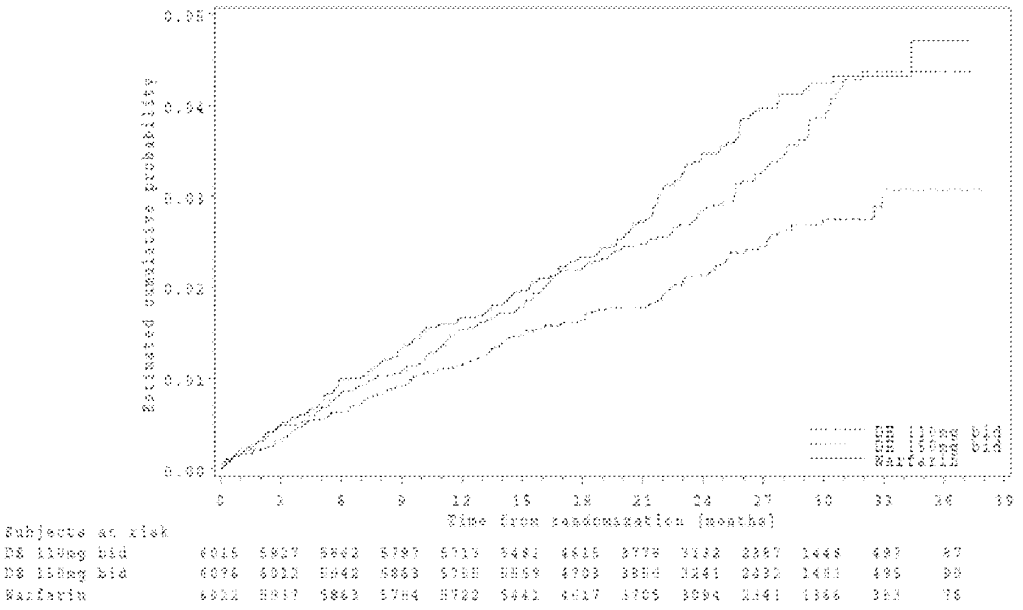


Figure 2.5.4.6: 1 Kaplan-Meier estimate of time to first stroke/SEE

Source data: 1160.26 [U09-3249-01], Figure 15.2.1.1: 1

Non-inferiority of both dabigatran doses compared to warfarin was demonstrated, using the Hochberg procedure to account for multiple comparisons (Table 2.5.4.6: 2). The hazard ratio for stroke/SEE for DE 110/warfarin was 0.91, with the 95% confidence interval (CI) of (0.75, 1.12). The hazard ratio for DE 150 mg/warfarin was 0.66 (95% CI 0.53, 0.82). The upper bound of the 95% CI is below 1.46, the protocol specified margin, for both doses. The p-value for the non-inferiority test, using 1.46, was <0.0001 for both doses. Relative risk reductions for stroke/SEE by DE 110 and DE 150 were 9% and 34%, respectively, in comparison to warfarin.

The upper bound of the 95%CI for both doses was also less than a non-inferiority margin of 1.38, which has been suggested as the correct margin for warfarin non-inferiority trials by calculating the risk ratios on a logarithmic scale (Jackson et al., [R08-2662]). This approach differs from the RE-LY calculation, which calculated the margin based on the hazard ratio instead of the log of the hazard ratio.

The high dose of dabigatran, DE150, was superior to warfarin for the primary endpoint of stroke/SEE, as demonstrated in a superiority test after non-inferiority was established. DE110 was not statistically superior to warfarin (p-value =0.3701). The two sided p-value for testing the superiority of DE150 to warfarin was 0.0002, statistically significant adjusting for multiple tests at $\alpha = 0.0125$ (Table 2.5.4.6: 2). The clarity of the results is shown graphically in Figure 2.5.4.6: 2.

Table 2.5.4.6: 2 Hazard ratios and CIs for composite endpoint of stroke/SEE

	DE 110 vs Warfarin	DE 150 vs Warfarin
Non-Inferiority Analysis		
Hazard ratio (SE)	0.91 (0.09)	0.66 (0.07)
95% CI	0.75, 1.12	0.53, 0.82
97.5% CI	0.72, 1.15	0.51, 0.84
P-value for non-inferiority using 1.46	<.0001	<.0001
P-value for non-inferiority using 1.38	<.0001	<.0001
Superiority Analysis		
P-value for superiority	0.3701	0.0002

Source data: 1160.26 [U09-3249-01], Table 15.2.1.1: 3, Table 15.2.1.1: 4 and Table 15.3.5.4: 4

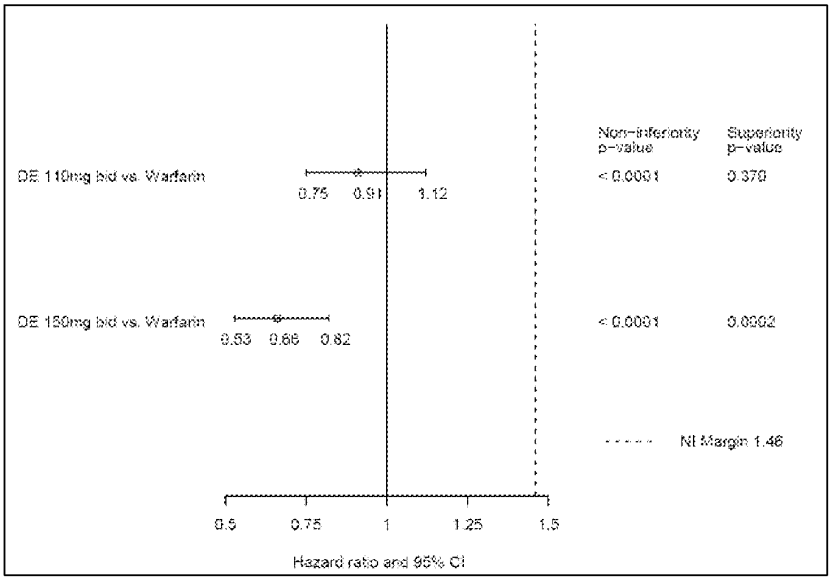


Figure 2.5.4.6: 2 Non-inferiority analysis for primary endpoint (stroke/SEE) in RE-LY.

The prespecified non-inferiority margin was 1.46.
Source data: SCE Appendix 6, Tables 2.1.1.1.5 and 2.1.1.1.11

Based on these results, the RE-LY study has achieved the prespecified objective for efficacy. Non-inferiority to warfarin was clearly demonstrated for both dabigatran doses in reducing the occurrence of stroke/SEE in subjects with AF and at least one additional risk factor for stroke.

The finding of superiority of dabigatran over warfarin was somewhat surprising in view of warfarin's large effect versus placebo and the results of recent trials. Warfarin reduces stroke by 62-64% compared to placebo, a substantial benefit. Recent trials of other compounds have

either been less effective (clopidogrel/ASA in ACTIVE-W), similar but with more bleeding (idraparinux in AMADEUS), or similar but with less bleeding (ximelagatran in SPORTIF trials). Thus the finding of increased benefit is unexpected.

There is some suggestion from event rates and pharmacodynamics in the Phase II trials and literature data on ximelagatran that dabigatran has a stronger anticoagulant effect than the dose of ximelagatran used in SPORTIF trials, where ximelagatran and warfarin had similar primary event rates. In study 1160.20, PETRO, the 150 mg bid dose of dabigatran showed a strong anticoagulant effect. Peak changes in aPTT with 150 mg bid are approximately 1.8 times control and trough values are approximately 1.4 times control. In comparison, 36 mg bid ximelagatran effects on aPTT are 1.4 times at peak and 1.1 times at trough. (Carlsson et al., [R09-1510]). Extrapolating from aPTT effects as a surrogate of anticoagulant activity, DE150 should be more efficacious than 36 mg bid ximelagatran. The long-term exposure to dabigatran 150 mg bid in Phase II (1160.42, PETRO-EX [U09-3247-01]) also demonstrated stroke/SEE rates of 1.3% per year, quite similar to the 1.1%/year obtained in RE-LY.

The trial size and the dose selection were both important aspects of the RE-LY primary efficacy results. Recruitment of over 18,000 subjects ensured good power for the primary endpoint, although the original planned trial size of 15,000 subjects and 450 adjudicated events were sufficient to show both the non-inferiority of both doses and the superiority of the high dose compared to warfarin ([SCE Appendix 6, Table 2.1.1.2.3]).

The demonstration of dose-response of dabigatran for the primary endpoint further strengthens the reliability of the evidence for the effectiveness of dabigatran in this indication. A single non-inferiority trial as the basis for efficacy normally compares one test treatment against standard of care. It rests upon a single comparison of two treatments. However, RE-LY provides two separate, independent, and blinded comparisons against the control group. The fact that both comparisons independently meet the non-inferiority margin is added assurance that the clinical effect of dabigatran compared to warfarin is reproducible and reliable. The dose response in efficacy further substantiates that dabigatran is an active treatment in the prevention of stroke and systemic embolism.

2.5.4.6.1 Components of the Primary Endpoint

The primary endpoint is a composite of ischemic and hemorrhagic stroke, and non CNS systemic embolism. The superiority of the DE150 dose over warfarin was reflected in all components of the primary endpoint (Table 2.5.4.6: 1).

For the non-inferiority of the DE110 dose, all the components of the composite were reduced compared to warfarin, except that the point estimate of the ischemic stroke rate was slightly higher than that for warfarin.

Hemorrhagic Stroke

For the component of hemorrhagic stroke, there was a strong treatment effect. Hemorrhagic stroke decreased by over 2/3 compared to warfarin for both doses and did not show dose-response. This finding was unexpected but it is of utmost clinical relevance since hemorrhagic strokes are the most devastating side effect of anticoagulation, leading to death in 50% of cases and significant morbidity in the remainder. A further discussion of the occurrence of hemorrhagic strokes is found in the safety section, together with intracranial bleeding, as well as in the section on net clinical benefit.

Table 2.5.4.6.1: 1 Hazard ratios and CIs for hemorrhagic stroke

	DE 110 mg bid vs Warfarin	DE 150 mg bid vs Warfarin
Hazard ratio (SE)	0.31 (0.09)	0.26 (0.08)
95% CI	0.17, 0.56	0.14, 0.49
p-value	0.0001	<0.0001

Source data: 1160.26 [U09-3249-01], Table 15.3.2.1: 9

Ischemic Stroke and SEE

Both ischemic stroke and SEE, the thromboembolic components of the primary endpoint, decreased compared to warfarin with the DE150 dose. For ischemic stroke, the reduction compared to warfarin was 24%, which was significant (p=0.034), [SCE Appendix 6, Table 2.1.1.1.13]. The reduction for SEE was similar, 33%, but was not significant, likely due to the small number of events [SCE Appendix 6, Table 2.1.1.1.23].

For DE110, the hazard ratio vs. warfarin for ischemic stroke was 1.14, but this difference was not significant (p=0.258). The hazard ratio for SEE was 0.73, also not significant. The DE150 effect on ischemic stroke was much greater than for DE110 (hazard ratio DE110 vs, DE150, 1.51, p=0.0012). [SCE Appendix 6, Tables 2.1.1.1.13 and 23]

The impact of the high dose of dabigatran on ischemic stroke is important because it indicates that the advantage of dabigatran compared to warfarin is not limited to effects on bleeding. The primary endpoint is a mixture of bleeding and thrombotic components. Dabigatran affects both components.

Stroke Severity

Stroke severity is a key determinant of disability and sequelae. Strokes in subjects with AF tend to be more disabling than other strokes. In RE-LY, approximately 50% of the strokes were disabling based on evaluations 3-6 months after the events. A Rankin score of 0-2 is generally regarded as non-disabling stroke, with scores of 3-6 considered as disabling stroke (a score of 6 is death). When comparing the numbers of disabling and/or fatal strokes between the treatment groups, the results were similar to the overall stroke results, namely the lowest rate was for D150 and similar or slightly fewer events on D110 compared to warfarin [SCE Appendix 6, Table 2.1.1.1.10]. Thus, the beneficial effect of dabigatran applies to both

severe and disabling strokes, as well as non-disabling strokes and as such is clinically relevant.

Stroke after Treatment Discontinuation

When evaluating the safety dataset, which is restricted to events occurring on treatment or within 6 days of treatment discontinuation, dabigatran effects were larger compared to warfarin. Of all first strokes, 59.9% (109/182), 56.4% (74/131), and 75.8% (150/198) occurred on treatment for DE110, DE150, and warfarin, respectively. Both strokes and strokes/SEEs were more frequent after dabigatran treatment discontinuation than after warfarin discontinuation ([SCE Appendix 6, Tables 2.1.1.1.3, and 2.1.1.1.9]). Within 6 days of drug discontinuation, there were 13, 10 and 6 strokes/SEEs for DE110, DE150 and warfarin respectively. Similarly, after 6 days off drug there were 61, 52, and 42 events, respectively. Approximately half of these strokes occurred 90 days or more off drug. The slight excess of strokes within the first 6 days of discontinuation of dabigatran may reflect its shorter half-life compared to warfarin. Warfarin effects last at least 3-5 days after stopping treatment whereas the half-life of dabigatran is 12-17 hours. After 1 day of stopping dabigatran (2 doses), approximately 75% of the drug is excreted. We conclude that the on treatment analysis (safety set) shows an even stronger effect of dabigatran compared to warfarin than the intention-to-treat analysis. Strokes occur after treatment discontinuation of warfarin and dabigatran.

2.5.4.6.2 Primary endpoint analysis by subgroup

In subgroup analyses of the primary endpoint, there were no significant interactions of the demographic characteristics with treatment (Figure 2.5.4.6.2: 1; only the figure for DE150 is reproduced in this overview). Age, gender, weight, BMI, renal function, previous exposure to VKAs, ethnicity and geographic region did not significantly affect the hazard ratios of dabigatran and warfarin. Stroke rates generally increased with age and decreased with creatinine clearance. Regionally, the stroke rates were highest in Asia and ethnically were also highest in Asians with one exception (1160.26 [U09-3249-01], Table 11.4.1.4.1: 1). However, the benefits of dabigatran compared to warfarin did not change.

2.5 CLINICAL OVERVIEW

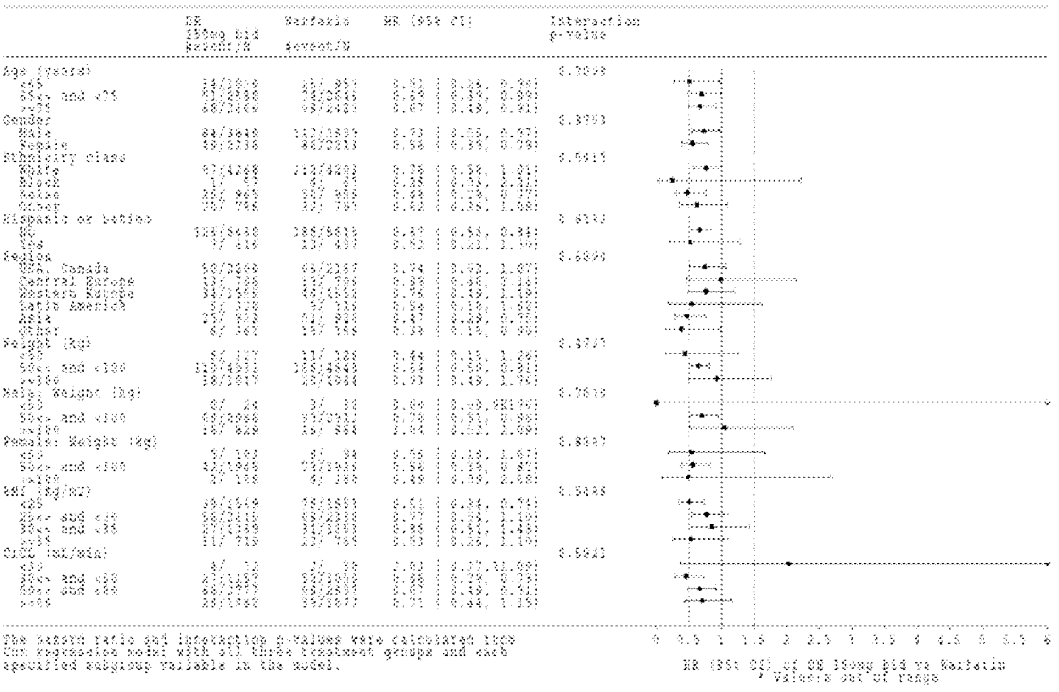


Figure 2.5.4.6.2: 1 Hazard ratio and 95% CI for stroke/SEE comparing DE 150 to warfarin by baseline demographic subgroups

Source data: 1160.26 [U09-3249-01], Table 15.2.3.2: 2

The stroke risk factors, when examined individually or together using $CHADS_2$ scores, also did not appreciably affect the relative benefits of both dabigatran doses (1160.26 [U09-3249-01], Figures 11.4.1.4.1: 4 and 5; Table 2.5.4.6.2: 1). Only the risk factor of age ≥ 65 years and hypertension showed a significant interaction with the DE110 dose versus warfarin. However, no such interaction was observed for the high dose, suggesting that the difference for the low dose was a chance occurrence.

Table 2.5.4.6.2: 1 Yearly event rate (%) for stroke/SEE by $CHADS_2$

	DE 110		DE 150		Warfarin	
CHADS2	# of subject	Event rate	# of subject	Event rate	# of subject	Event rate
1	1809	1.12	1815	0.65	1707	1.06
2	2088	1.43	2136	0.84	2229	1.35
3^+	1966	2.12	1979	1.88	1931	2.68

Source data: 1160.26 [U09-3249-01], Table 15.2.3.4: 3 and SCE Appendix 6, Table 3.5.1

Overall the benefits of dabigatran compared to warfarin in the primary endpoint were remarkably stable over a wide range of demographic and disease characteristics. The consistency of effect across subgroups further supports the effectiveness of dabigatran in this subject population.

2.5.4.6.3 INR control subgroups

A post hoc analysis of interest is the impact of INR control on the warfarin event rates. If dabigatran was non-inferior only to poor quality warfarin treatment, it could imply that it is less effective than normal standard of care. These analyses do show that poorer INR control on warfarin, defined as time in therapeutic range (TTR), is associated with higher event rates. Indeed, dabigatran compares quite favorably with this subgroup, with better hazard ratios for the primary endpoint than for the overall analysis. Both doses have an upper bound of the 95% CI that is less than 1, indicating superiority (Table 2.5.4.6.3: 1). Thus, both doses of dabigatran are superior to poorly controlled warfarin.

However, the benefits of dabigatran also remain when compared with the subset of well-controlled warfarin (TTR ≥65%). The DE150 treatment remains superior and the DE110 treatment is non-inferior to well-controlled warfarin, even in a subgroup analysis using the more conservative non-inferiority margin of 1.38 (Table 2.5.4.6.3: 1).

The effectiveness of dabigatran treatment is thus established independent of the levels of warfarin INR control attained in this trial. The time in therapeutic range for warfarin in RE-LY is similar to other contemporary AF trials of antithrombotic agents. For a non-inferiority trial, it is reassuring that even compared to a post hoc defined subset of well-controlled subjects, the non-inferiority and superiority findings are still maintained. This is further substantiation of the efficacy of dabigatran.

Table 2.5.4.6.3: 1 Hazard ratios and 95% CIs for composite endpoint of stroke/SEE by INR control for warfarin- Safety Set

	Mean % of time of INR in range 2-3 ≥ 65%	
	DE 110 vs Warfarin	**DE 150 vs Warfarin**
Hazard ratio (SE)	1.03 (0.15)	0.69 (0.11)
95% CI	0.77, 1.37	0.50, 0.93
	Mean % of time of INR in range 2-3 <65%	
	DE 110 vs Warfarin	**DE 150 vs Warfarin**
Hazard ratio (SE)	0.74 (0.10)	0.49 (0.08)
95% CI	0.56, 0.97	0.36, 0.67

The analyses included all DE subjects, and different warfarin subjects for each group.
Source data: 1160.26 [U09-3249-01], Tables 15.2.1.2: 14 and 15.2.1.2: 16

2.5.4.6.4 Effect of Baseline and Concomitant Medication Use

Antithrombotics

Analyses of subgroups using baseline medications generally showed no significant interactions with treatment on the primary endpoint, with the exception of ASA/clopidogrel and the group of drugs classified as P-gp inhibitors (1160.26 [U09-3249-01] Table 15.2.3.3: 1

and 15.2.3.3: 3). ASA/clopidogrel use likely identifies a group of subjects with coronary disease in addition to AF. The hazard ratios for the primary endpoint (DE 110 vs. warfarin and DE 150 vs. warfarin) decreased by at least 50% for subjects on ASA/clopidogrel at baseline. The reason for a decrease in relative risk of dabigatran compared to warfarin in this subset is not clear. During treatment, there were only ~120 subjects per group who were on ASA/clopidogrel at least 50% of the time. The number of events is small. The clinical relevance of this finding should be interpreted with caution.

ASA use at baseline was associated with higher stroke/SEE rates in these subjects during the trial but there was no treatment interaction (1160.26 [U09-3249-01] Figures 15.2.3.3: 4 and 5). Similarly, ASA use during treatment was associated with higher event rates (stroke/SEE) but there was no treatment interaction.

The concomitant use of these antiplatelet agents with the randomized treatments was less frequent than at baseline. During the trial the usage of concomitant ASA was ~25% (on ASA at least half the time in the trial). This frequency of concomitant ASA use in an anticoagulation trial is extremely high compared to other recent trials (for SPORTIF III + V, 14.5% used ASA at least 50% of the time, [P06-11789]). Antiplatelet use on a background of anticoagulation increases the risk of bleeding for warfarin and dabigatran [P06-11789, P07-11021]. Based on this, the absolute bleeding rates in RE-LY should be higher than those observed in ACTIVE-W and the SPORTIF trials.

P-glycoprotein Inhibitors

In the subgroup taking P-gp inhibitors at baseline, for both doses of dabigatran the hazard ratio versus warfarin for the primary endpoint of stroke/SEE was approximately 50% lower ($p=0.0082$ for interaction, [SCE Appendix 6, Table 3.3.3]. For the most commonly used P-gp inhibitors (verapamil, diltiazem, and amiodarone), there were 1,300 to 2,700 subjects exposed to these medications during the trial.

With concomitant use of verapamil, a strong P-gp inhibitor, the rate of stroke/SEE and ischemic stroke in dabigatran subjects compared to warfarin tended to be lower, suggesting an interaction (1160.26 [U09-3249-01], Table 15.2.3.3: 4 and 5) but this must be interpreted with caution. At baseline, verapamil did not interact with treatment (1160.26 [U09-3249-01], Table 15.2.3.3: 3). In addition, if there is an effect of P-gp inhibition by verapamil causing clinically relevant increased exposure, then it should be apparent in bleeding rates. Major bleed rates on verapamil were slightly elevated compared to warfarin but only for the high dose (2.64%/year, 3.04, and 3.35 for no use of verapamil in DE 110, DE 150, and warfarin respectively; 2.06%/year, 4.24, and 3.19 for the subjects always on verapamil, (1160.26 [U09-3249-01], Table 15 3.2.2.3: 3). However, for any bleeds, a more sensitive indicator for elevated plasma concentrations due to a larger number of events, there was no evidence of increased bleeding rates on verapamil (14.7%/year, 16.5, and 18.1 for no use of verapamil in DE 110, DE 150, and warfarin respectively; 13.9%/year, 15.2, and 17.5 for the subjects always on verapamil, (1160.26 [U09-3249-01], Table 15.3.2.2.3: 5). Thus, the use of verapamil and dabigatran together was not consistently associated with an increased bleed rate but was associated with a decreased rate of stroke. These findings do not suggest a

clinically relevant increase in exposure when verapamil and dabigatran are administered concomitantly.

For amiodarone, a strong P-gp inhibitor, there was also a lower rate of stroke in dabigatran subjects always taking this medication compared to warfarin (1160.26 [U09-3249-01], Table 15.2.3.3: 4 and 5). However, there was no increase in the rates of major bleeding or any bleeding (1160.26 [U09-3249-01], Table 15 3.2.2.3: 3 and 5). This suggests there was no clinically relevant increase in exposure when amiodarone and dabigatran were administered together.

For diltiazem, a moderate to weak P-gp inhibitor, there was no evidence of an interaction with dabigatran treatment on the rate of stroke/SEE or on bleeding.

2.5.4.7 EFFICACY—SECONDARY ENDPOINTS

2.5.4.7.1 Stroke/SEE/death

The treatment effects of dabigatran were also reflected in all specified secondary endpoints. The risk reductions on stroke/SEE and death were 7% for DE 110 compared to warfarin, which was not statistically significant, and 17% for DE 150, which was statistically significant (p-value = 0.0018).

Table 2.5.4.7.1: 1 Hazard ratios and 95% CIs for composite endpoint of stroke/SEE/death

	DE 110mg bid vs Warfarin	DE 150mg bid vs Warfarin
Hazard ratio (SE)	0.93 (0.05)	0.83 (0.05)
95% CI	0.83, 1.05	0.74, 0.93
P-value	0.2448	0.0018

Source data: 1160.26 [U09-3249-01], Table 15.2.2.1: 2

The secondary endpoint of stroke/SEE/death allows an assessment of the impact of mortality on the primary clinical outcome. Death is an important competing risk in AF subjects compared to stroke since AF subjects have a mortality rate of 3.5-4.0%, even when on treatment with warfarin. Warfarin reduces mortality in AF subjects by 33% compared to placebo (AFI meta-analysis, [P05-06213]). When warfarin INR is maintained above 2.0, it reduces the risk of death over 3-fold compared to lower INRs (Hylek, [R03-2309]). In the historical placebo-controlled trials the composite endpoint of stroke/SEE/death was decreased 48% by warfarin [P05-06213].

Essentially the effect of dabigatran compared to warfarin on the risk of stroke/SEE/death was similar to that obtained with the primary endpoint. The low dose was non-inferior to warfarin and the high dose was superior to warfarin (p=0.0018). DE 110 was approximately 13% less effective than DE 150 (p=0.0491), (1160.26 [U09-3249-01], Table 15.2.2.1: 2).

2.5.4.7.2 Mortality

Mortality was evaluated as a standalone outcome. The yearly rate for all cause death was 3.74%, 3.63% and 4.13% DE 110, DE 150 and the warfarin groups, respectively (Table 2.5.4.7.2: 1). Overall, 1,372 deaths occurred. Both dabigatran treatments reduced the risk of all cause mortality. The risk reductions by DE 110 and DE 150 were 10% (p-value=0.1232) and 12% (p-value=0.0475), respectively. Most of this effect was due to vascular death. This is a clinically relevant finding since, as mentioned, warfarin reduces mortality in AF subjects compared to placebo. An additional reduction in mortality over and above the effect of warfarin is clinically important and further substantiates the advantages of dabigatran compared to warfarin.

Table 2.5.4.7.2: 1 Yearly event rate (%) for death in Study 1160.26

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Randomized	6015	6076	6022
Subject-years	11900	12039	11797
Death*	445 (3.74)	437 (3.63)	487 (4.13)
Vascular	288 (2.42)	273 (2.27)	317 (2.69)
Sudden Cardiac	109 (0.92)	93 (0.77)	103 (0.87)
Non-Sudden Cardiac	68 (0.57)	68 (0.56)	71 (0.60)
Hemorrhagic	9 (0.08)	13 (0.11)	17 (0.14)
Other vascular	46 (0.39)	45 (0.37)	58 (0.49)
Unknown	56 (0.47)	54 (0.45)	68 (0.58)
Non-vascular	157 (1.32)	164 (1.36)	170 (1.44)

* after database lock, 2 additional deaths were identified. Their impact is discussed in section 2.5.5.6
Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint. (Subject 31020 is included).
Subject-years = sum(date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100
Source data: SCE Appendix 6, Table 2.1.1.3.1

The risk of death in AF subjects on Vitamin K antagonists is strongly associated with the level of INR control. Poor control increases the risk of death by a factor of 3 or more (Hylek, [R03-2309]). Correspondingly, the mortality benefit of dabigatran over warfarin was restricted to the subjects who were poorly controlled on warfarin. For TTR<60%, the hazard ratio was 0.73 for both doses of dabigatran compared to warfarin (95% CI 0.58 to 0.92 and 0.59 to 0.92, respectively). For TTR≥60% the hazard ratios were 0.99 and 0.96 (SCE Appendix 6, Table 3.6.10).

For vascular death, there is a 33% reduction with DE150 compared to warfarin (hazard ratio=0.67, 95% CI 0.51 to 0.88; SCE Appendix 6, Table 3.6.15). The risk reduction for DE110 vs. warfarin was 0.77 but it was not statistically significant (95% CI 0.59 to 1.01).

This is a post hoc analysis since one cannot *a priori* predict who will or will not be well controlled on warfarin. Nevertheless, this finding identifies a population of warfarin treated subjects who would greatly benefit from dabigatran treatment.

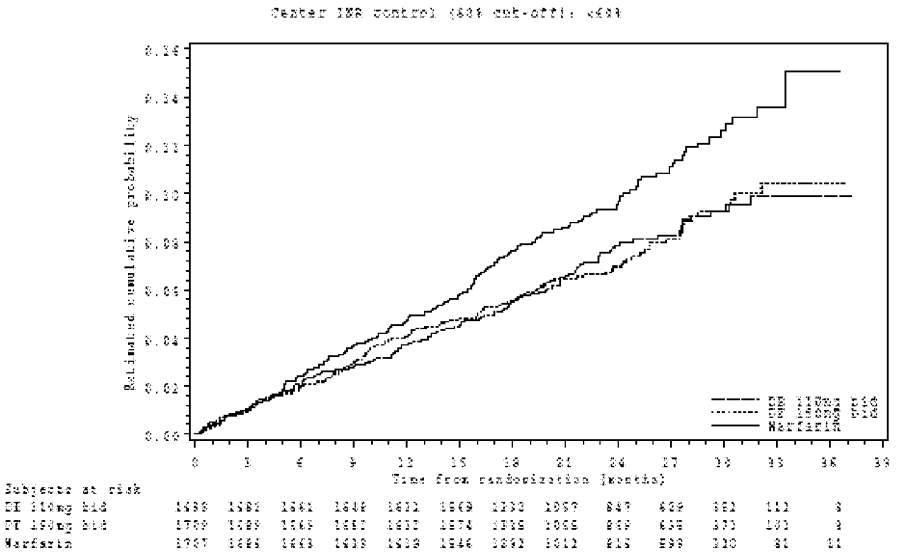


Figure 2.5.4.7.2: 1 Part A: Time to death by Center INR Control <60%

Source data: SCE Appendix 6, Figure 3.6.7

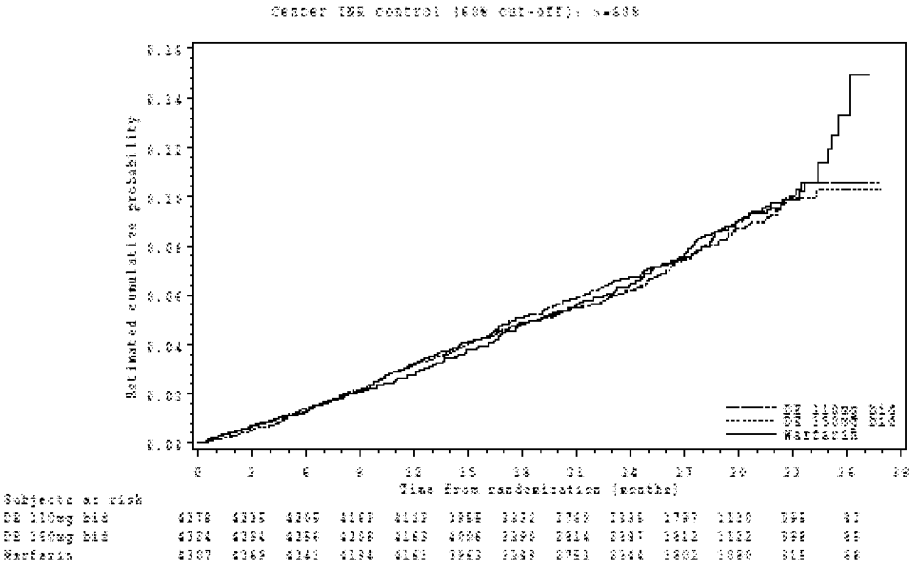


Figure 2.5.4.7.2: 2 Part B: Time to death by Center INR Control >60%. There are no treatment differences

Source data: SCE Appendix 6, Figure 3.6.7

2.5.4.7.3 Other Composite Endpoints

Cardiovascular disease burden is a key determinant of the morbidity and mortality of AF. When vascular death is incorporated into a composite outcome with other cardiovascular clinical outcomes, namely PE, MI, stroke and SEE, the benefits of dabigatran compared to warfarin still remain, with the high dose superior to warfarin (hazard ratio 0.85, p=0.0151, (SCE Appendix 6, Table 2.1.1.4.2).

The combination of all the cardiovascular outcomes is a valuable assessment of the overall benefits of dabigatran compared to warfarin. It also helps to put into perspective the slightly higher rates of myocardial infarction in the dabigatran treatment arms (see below). The slightly higher incidence of MI on dabigatran is more than counterbalanced by the other cardiovascular endpoints. DE 150 still remains superior to warfarin.

Another composite secondary endpoint (ischemic stroke, SEE, PE, MI, TIA, all deaths and hospitalization) also confirmed the benefit of dabigatran. The yearly event rate for this composite endpoint was dominated by hospitalizations (19.4%, 20.2% and 20.8% for DE 110, 150 and warfarin, respectively, [SCE Appendix 6, Table 2.1.1.5.1]. The DE 110 bid was superior to warfarin for this composite endpoint. Hazard ratios for DE 110 bid and DE 150 bid vs. warfarin were 0.92 and 0.97 (p-values=0.0021 and 0.3075), respectively [SCE Appendix 6, Table 2.1.1.5.2].

2.5.4.7.4 Other Individual Components of Composite Endpoints

Pulmonary Embolism

The frequency of pulmonary embolism in this population was small (43 total events, [SCE Appendix 6, Table 2.1.1.5.1]). Pulmonary emboli were more frequent on dabigatran compared to warfarin (HR 1.26 and 1.61 for DE110 and DE 150, respectively) but the differences were not significant (p=0.560 and p=0.214) [SCE Appendix 6, Table 2.1.1.1.24].

Myocardial Infarction

The rate of MI was higher in the dabigatran groups compared to the warfarin group. The yearly event rates were 0.72%, 0.74% and 0.53% for DE 110, DE 150 and warfarin, respectively (p=0.07 and p=0.049 for DE 110 vs. warfarin and DE150 vs. warfarin). Based on the on treatment analysis (safety set), the event rates were slightly lower (0.68%, 0.69% and 0.49% respectively) and the differences between dabigatran and warfarin were not significant (p=0.066 and p=0.055) [SCE Appendix 6, Table 2.1.1.4.4].

Subjects with pre-existing CAD (~28%), HF (~32%), or those on ASA had a higher rate of occurrence of MI than other subgroups but the relative risk differences in favor of warfarin remained. The rate of MI in Asians was somewhat lower and did not differ across treatments. The overall rate of MI was not large compared to rates of stroke or death in this trial or to rates of MI in a CAD population. The differences between dabigatran and warfarin were observed for both doses. In subjects who did not use ASA, clopidogrel, or the combinaton, there was no difference in the risk of MI across treatments. Use of these agents may reflect coronary disease (1160.26 [U09-3249-01, Tables 15.2.5: 4, 6, 12 and 13].

2.5 CLINICAL OVERVIEW

The total numbers of patients with MIs in the primary analysis (randomized set) were 86, 89, and 63 for DE 110, DE 150, and warfarin, respectively (SCE Appendix 6, Table 2.1.1.5.1). When the time of occurrence of MI was evaluated, the number of MIs on treatment was nearly the same across treatments though still slightly more on dabigatran (1.1%, 1.1%, and 0.9 % of subjects for DE 110, DE 150, and warfarin, respectively (SCE Appendix 6, Table 2.1.1.4.5). However, there were 13, 11, and 6 MIs that occurred within 6 days of discontinuation of DE 110, DE 150, and warfarin, repectively. When the events that were recorded as occurring 1-6 days off treatment were closely evaluated, more than half of these events occurred or started on treatment. Some of the difference across treatments was due to events occurring more than 6 days off-treatment. More MIs occurred more than 6 days off-treatment in the dabigatran groups by a ratio of approximately 1.7:1 (17, 21, and 11 events for DE110, DE150 and warfarin, respectively) (1160.26 [U09-3249-01] Table 15.2.5: 15). There was also variability in the use of non-study oral anticoagulants after treatment discontinuation so it is difficult to interpret the meaning of this off-treatment difference.

The pattern and type of MI as reported by the investigator did not differ in most characteristics. There was a lower frequency of MIs with Q-wave or ST-changes on dabigatran. However, the numbers are small and no firm conclusions can be drawn.

To assess whether there is difference across treatments in the risk of coronary events other than MI, we used a MeDRA query to search for all terms for coronary ischemia. The incidence of these other coronary ischemic events was compared across treatments in all subjects except those who had MIs. The incidence was 2.6%, 2.3%, and 2.7% for DE 110, DE150 and warfarin, respectively (SCS Appendix 7, Tables 2.1.1.2.4.1-3). Thus, there is no indication of any imbalance in additional symptoms of ischemic coronary disease by treatment. Including subjects with MIs did not relevantly change the differences between treatments.

In the context of other cardiovascular events, namely vascular death, PE, stroke and SEE, the increased in frequency of MI on dabigatran is counterbalanced by the reduction in other events. The benefits of dabigatran compared to warfarin still remain, with the high dose superior to warfarin (hazard ratio 0.85, p=0.0151, [SCE Appendix 6, Table 2.1.1.4.2].

Another frequently used composite endpoint in cardiovascular trials is MACE (major adverse cardiac events). In non-interventional trials, this is normally a composite of stroke, non-fatal MI and cardiovascular death. When cardiovascular outcomes are evaluated with this composite, the DE110 dose is similar to warfarin (hazard ratio 1.01) and the DE150 dose is superior (hazard ratio 0.84, p=0.022) (Tables 2.5.4.7.4: 1 and 2.5.4.7.4: 2).

Table 2.5.4.7.4: 1 Yearly event rate (%) for MACE in Study 1160.26

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Randomized	6015	6076	6022
Subject-years	11900	12039	11797
MACE	402 (3.38)	340 (2.82)	394 (3.34)
Cardiovascular death	177 (1.49)	161 (1.34)	174 (1.47)
Stroke	171 (1.44)	121 (1.01)	184 (1.56)
Fatal Stroke	23 (0.19)	24 (0.20)	36 (0.31)
MI	86 (0.72)	89 (0.74)	63 (0.53)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint.
Subject-years = sum(date of study termination – date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100
Source data: [SCS Appendix 7, Table 2.1.3.3.1]

Table 2.5.4.7.4: 2 Hazard ratios and 95% CIs for MACE in Study 1160.26

	DE 110mg bid vs Warfarin	DE 150mg bid vs Warfarin
Hazard ratio (SE)	1.01 (0.07)	0.84 (0.06)
95% CI	0.88, 1.06	0.73, 0.98
P-value	0.8639	0.0216

Source data: [SCS Appendix 7, Table 2.1.3.3.4]

The reasons for the different rates of MI on dabigatran and warfarin are not immediately clear. In subjects receiving dabigatran without ASA in the Phase II PETRO trial (1160.20), there was a non dose-related increase in urinary thromboxane, a possible marker for platelet activation. However, this effect was not seen in subjects taking dabigatran + ASA in the Phase II study. In RE-LY, the frequency of MI on dabigatran and warfarin was highest in the group co-medicated with ASA, with the relative risk difference persisting in favor of warfarin (RE-LY, 1160.26 [U09-3249-01], Table 15.2.5: 13).

In RE-LY almost 30% of subjects had pre-existent coronary disease and 16% had a previous MI. Thus, it is expected that coronary events will occur in this population. In AF subjects in ACTIVE-W warfarin was more effective than ASA/clopidogrel with an even higher risk ratio than in this trial (Table 2.5.4.7.4: 3). However, the finding was not significant, perhaps due to the smaller trial size. In the SPORTIF trials with another direct thrombin inhibitor, ximelagatran, there was a higher rate of MI on ximelagatran in SPORTIF III but a lower rate in SPORTIF V. The table shows MI rates in recent AF trials, by treatment. The MI rates in RE-LY are consistent with other trials in AF.

Table 2.5.4.7.4: 3 MI rates in AF trials (event rate per 100 subject-years)

Trial	N	warfarin	dabigatran	ximelagatran	clopidogrel+ ASA	ASA	idraparinux
RE-LY	**18,113**	**0.53**	**0.72, 0.74**				
ACTIVE-W	6,706	0.55			0.86		
ACTIVE-A	7,554				0.70	0.90	
AMADEUS	4,576	0.6					0.8
SPORTIF III	3,410	0.6		1.1			
SPORTIF V	3,922	1.4		1.0			
BAFTA	973	1.1				1.2	
AFFIRM*	4,060	0.99					

* 140 MIs, mean exposure 3.5 years, estimated crude rate=0.99%/year
Source data: ACTIVE-A, [R09-1514]; ACTIVE-W, [P06-06455]; AFFIRM, [R09-1282]; AMADEUS, [P08-01644] BAFTA, [P07-09739]; SPORTIF V, [P05-01352]; SPORTIF III, [R03-2719] and [SCE Appendix 6, Table 2.1.1.4.1]

Warfarin is extremely effective in prevention of MI in a post-MI population (WARIS and WARIS-2 [R09-1516], [R03-1234]). Direct thrombin inhibitors (ximelagatran, hirudin) have been shown to be effective in preventing MI in an acute MI population (ESTEEM [R03-2266]) and in ACS subjects when used in place of heparin (HERO-2 [R09-1515]). Without a placebo-controlled trial of dabigatran, the source of the difference between warfarin and dabigatran cannot be determined.

We conclude that the incidence of MI in AF subjects treated with dabigatran is higher than the incidence in warfarin treated AF subjects.

2.5.4.8 EFFICACY CONCLUSIONS

- For the primary efficacy endpoint, stroke/SEE, non-inferiority for both doses of dabigatran with warfarin was established ($p < 0.0001$ for both comparisons) and DE 150 was superior to warfarin ($p=0.0002$). The relative risk reductions for DE 110 and DE 150 were 9% and 34%, respectively.

- Both doses of dabigatran significantly reduced the occurrence of hemorrhagic stroke compared to warfarin ($p<0.0001$). The relative risk reductions were 69% and 74% for DE110 and DE150 compared to warfarin.

- Ischemic stroke was reduced by 24% for DE150 compared to warfarin, $p=0.034$.

- Dabigatran was equally effective in preventing disabling and non-disabling stroke.

- The superiority of the DE150 dose to warfarin was maintained even when compared to a subset of warfarin subjects with good INR control (TTR≥60% or 65%).

- The risk of death (all cause and vascular) was lower for both doses of dabigatran compared with warfarin. All cause mortality was reduced by 12% for DE150 compared to warfarin, $p=0.0475$. Most of this effect was due to a reduction in vascular death (15%, $p=0.0386$). In a post-hoc subgroup analysis, the benefit was greatest when dabigatran was compared to subjects with poorer INR control. Vascular death was reduced 33% by DE150 compared to warfarin subjects with poorer INR

control. *(Note that after database lock 2 additional deaths were identified in the DE 150 group. The impact of these are discussed in Section 2.5.5.6)*

- The low dose of dabigatran was similar to warfarin and DE 150 was superior to warfarin for the secondary efficacy endpoints (stroke/SEE/death and stroke/SEE/PE/MI/vascular death). The risk reduction by DE 110 for stroke/SEE/death was 7% in comparison to warfarin, not statistically significant, while the relative risk reduction by DE 150 was 17%, (p-value =0.0016). For stroke/SEE/PE/MI/vascular death, the 15% relative risk reduction for DE 150 vs. warfarin was significant (p=0.0151).

- For ischemic stroke, SEE, PE, MI, TIA hospitalization and all cause death the risk reductions were 8% and 3%, for DE 110 and DE 150, respectively, with corresponding p values of 0.002 and 0.3).

- The frequency of MI was higher in the dabigatran groups than in the warfarin group.

- When risk and benefit were considered (NCB endpoint) both dabigatran doses had smaller risk ratios compared to warfarin. Risk reduction for DE 110 and DE 150 were 8% and 10%, respectively with corresponding p values of 0.100 and 0.037. Yearly event rates were 7.08%, 6.89% and 7.63% for DE 110, DE 150 and warfarin groups, respectively.

- The efficacy of dabigatran was consistent for all subgroups evaluated. There were no significant by subgroup treatment interactions.

These data are highly clinically relevant, since superiority over warfarin in stroke prevention in AF patients has been demonstrated for the first time. This applies both in terms of stroke prevention and in terms of reduction of vascular mortality.

2.5.5 OVERVIEW OF SAFETY

As with any anticoagulant, the most important adverse event associated with dabigatran treatment is bleeding. Based on the pharmacological profile, this is an expected effect of the drug. While the safety analyses of the dabigatran clinical trials carefully analysed all laboratory and adverse event data, as well as vital signs, there were relatively few indications of any adverse reactions apart from bleeding. This section therefore focuses first on analysis of the bleeding events from clinical trials. The principal basis of this analysis, apart from dose-finding, was the RE-LY trial (1160.26) which contributed approximately 95% of the total exposure in AF subjects.

For adverse events other than bleeding, analyses were conducted for adverse events by System Organ Class, serious adverse events (SAEs), discontinuations due to adverse events, and adverse events leading to death. (All deaths were analysed by treatment in the Efficacy section as outcome events.) Laboratory data was analysed for trends, with most of the data coming from the large Phase III trial. Special emphasis was placed on monitoring of hepatic safety, including a pre-specified interim analysis of RE-LY after it had accrued a susbstantive fraction of long-term exposure to detect any signs of potential hepatotoxicity.

2.5.5.1 BLEEDING

The primary safety endpoint in Phase III was major bleeding. Bleeding events were analysed in several categories: major bleeds, defined based on the ISTH definition, and minor bleeds were the primary divisions of bleeding events. All major bleeds were blindly adjudicated. The composite of major+minor bleeding, any bleeds, was also analysed. The primary focus was on the major bleeds since these are by definition clinically more relevant than minor bleeds. They more often lead to discontinuation of treatment and are associated with greater morbidity.

Major bleeds were divided into life-threatening and non-life-threatening. Within life-threatening bleeds the most important category is intracranial hemorrhage (ICH), which is a composite of intracerebral hemorrhage (= hemorrhagic stroke), sub-arachnoid and subdural hemorrhage. These two bleeding categories (ICH and the hemorrhagic stroke component) are the clinically most relevant adverse consequences of anticoagulation and therefore deserve special attention. ICH is the only hemorrhagic complication that causes deficits as great or greater than the ischemic strokes that anticoagulants are intended to prevent. Fear of these devastating bleeding events is a primary factor in the under-prescribing of anticoagulation in AF subjects.

2.5.5.1.1 Phase II data

The duration and size of the Phase II trials were limited and provided only rough estimates of the bleeding rates associated with different dose regimens.

The PETRO trial (1160.20) demonstrated dose-response for bleeding over the range of 50 mg bid to 300 mg bid. In this 12 week trial, the bleeding rates of 150 mg bid and 300 mg bid without ASA were approximately the same. The addition of ASA increased bleeding rates

(Figure 2.5.5.1.1: 1). The 300 mg bid +ASA dose was stopped due to bleeding, thus defining a maximal tolerated dose.

With almost 2,000 patient years of exposure in the PETRO-EX trial (1160.42), the extension study, unacceptably high rates of major bleeding were seen with 300 mg bid without ASA. The major bleeding rates are illustrated together with the stroke rates in Figure 2.5.1.1: 1. The small Japanese Phase II trial 1160.49, showed that the bleeding rates with 110 mg bid and 150 mg bid were comparable to that of warfarin.Thus Phase II identified 110 mg bid and 150 mg bid as doses with acceptable bleeding rates and defined the maximal tolerated dose to be less than 300 mg bid.

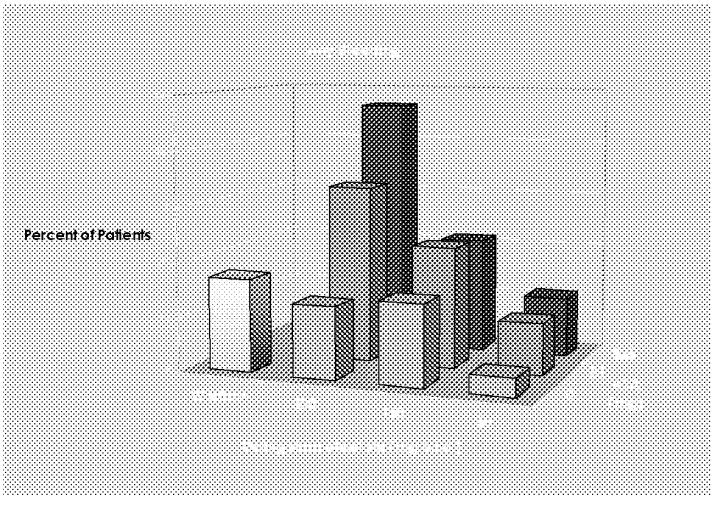


Figure 2.5.5.1.1: 1 Any bleeding rates by dabigatran dose and by ASA dose compared to warfarin in the PETRO trial (1160.20).

Source data: PETRO, 1160.20 [U06-1615] Table 12.2.2.3: 2

2.5.5.1.2 Phase III—RE-LY

The RE-LY trial had a mean duration of 24 months. Total exposure to dabigatran was in excess of 20,000 subject-years, with over 10,000 subject-years of exposure on warfarin [SCS Appendix 7, Table 1.1.2.2]. Thus estimates of bleeding rates from this trial are robust, with sufficient power to reliably detect differences much less than 1% per year in event rates.

Both doses of dabigatran were associated with lower rates of life-threatening major bleeds, including lower rates of hemorrhagic stroke and ICH compared to warfarin. In addition, both doses also had lower rates of minor bleeding and any bleeding compared to warfarin. The primary safety endpoint of major bleeding was significantly reduced by DE 110 compared to warfarin.

Table 2.5.5.1.2: 1 Yearly event rate of major bleeding events and other bleeding events in Study 1160.26 (randomized set)

	DE 110 bid N (%)	DE 150 bid N (%)	Warfarin N (%)
Adjudicated Bleeds			
Number of subjects	6,015	6,076	6,022
Subject-years	11,900	12,039	11,797
Major bleeds	318 (2.67)	375 (3.11)	396 (3.36)
Life threatening MBEs	143 (1.20)	175 (1.45)	210 (1.78)
Other MBEs	196 (1.65)	226 (1.88)	208 (1.76)
Haemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
ICH	25 (0.21)	36 (0.30)	85 (0.72)
Minor bleeds[a]	1,566 (13.16)	1,787 (14.84)	1,930 (16.36)
Any bleeds[a]	1,749 (14.70)	1,990 (16.53)	2,152 (18.24)

In case of recurrent event of the same category, the first event was considered. Minor bleeds were not adjudicated.
Subject-years = sum (date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.
[a] Investigator-reported bleeding events
Source data: SCS Appendix 7, Tables 2.1.1.1.1.3, 2.1.1.1.1.6 and SCE Appendix 6, Table 2.1.1.1.1.

Table 2.5.5.1.2: 2 Hazard ratio and 95% CI for bleeds in Study 1160.26 (randomized set)

		DE 110 bid vs Warfarin	DE 150 bid vs Warfarin	DE 110 bid vs DE 150 bid
Adjudicated major bleeds	Hazard ratio (SE)	0.79 (0.06)	0.93 (0.07)	0.85 (0.06)
	95% CI	0.68, 0.92	0.81, 1.07	0.73, 0.99
	P-value	0.0021	0.3222	0.0356
Investigator reported any bleeds	Hazard ratio (SE)	0.79 (0.03)	0.91 (0.03)	0.86 (0.03)
	95% CI	0.74, 0.84	0.86, 0.97	0.81, 0.92
	P-value	<.0001	0.0029	<.0001
Adjudicated hemorrhagic strokes	Hazard ratio (SE)	0.31 (0.09)	0.26 (0.08)	1.18 (0.46)
	95% CI	0.17, 0.56	0.14, 0.49	0.55, 2.55
	P-value	0.0001	<.0001	0.6743
Adjudicated life-threatening bleeds	Hazard ratio (SE)	0.67 (0.07)	0.82 (0.08)	0.82 (0.09)
	95% CI	0.54, 0.83	0.67, 1.00	0.66, 1.03
	P-value	0.0003	0.0470	0.0873
Adjudicated ICH	Hazard ratio (SE)	0.29 (0.07)	0.41 (0.08)	0.70 (0.18)
	95% CI	0.19, 0.45	0.28, 0.61	0.42, 1.17
	P-value	<.0001	<.0001	0.1738

In case of recurrent event, the first event was considered.
Source data: SCS Appendix 7, Table 2.1.1.1.1.14

2.5.5.1.3 Major Bleeds

The low dose of dabigatran DE 110 was associated with 21% less major bleeding than warfarin, while the high dose DE 150 had 7% less major bleeding. Over twice as many bleeds

on warfarin were symptomatic bleeding into a critical area/organ (Table 2.5.5.1.3: 1). These bleeds were classified as life-threatening. Fatal bleeding events also occurred more frequently on warfarin (8.6% of major bleeds) than on dabigatran (6.6% for DE 110 and 6.1% for DE 150). Notably, there were more gastrointestinal major bleeds on dabigatran than there were on warfarin. These are discussed below.

Table 2.5.5.1.3: 1 Major bleeds by bleeding criteria in Study 1160.26 (randomized set)

	DE 110	DE 150	Warfarin
Total number of major bleeds	377 (100.0)	460 (100.0)	451 (100.0)
Hospitalized for the event	275 (72.9)	358 (77.8)	345 (76.5)
Bleeding criteria,			
Drop of Hemoglobin >=20 g/L	251 (66.6)	310 (67.4)	270 (59.9)
Required transfusion >= 2 units	229 (60.7)	304 (66.1)	238 (52.8)
Symptomatic bleeding in critical area/organ	54 (14.3)	65 (14.1)	136 (30.2)
Intraocular	13 (3.4)	9 (2.0)	16 (3.5)
Intraspinal	0	0	0
Intramuscular	7 (1.9)	8 (1.7)	16 (3.5)
Retroperitoneal	2 (0.5)	9 (2.0)	12 (2.7)
Intra-articular	3 (0.8)	3 (0.7)	6 (1.3)
Pericardial	1 (0.3)	3 (0.7)	3 (0.7)
Symptomatic intracranial	31 (8.2)	36 (7.8)	85 (18.8)
Subdural	13 (3.4)	21 (4.6)	38 (8.4)
Intracerebral	16 (4.2)	15 (3.3)	45 (10.0)
Gastrointestinal	150 (39.8)	209 (45.4)	132 (29.3)
Other area/organs	38 (10.1)	28 (6.1)	39 (8.6)
Associated with hypotension	18 (4.8)	34 (7.4)	22 (4.9)
Required surgical intervention	35 (9.3)	56 (12.2)	62 (13.7)
Fatal bleeding events	25 (6.6)	28 (6.1)	39 (8.6)

Source data: SCS Appendix 7, Table 2.1.1.1.1.7

2.5.5.1.4 Life-threatening Bleeds, ICH and Hemorrhagic Stroke

The relative reduction in life-threatening bleeds was 33% ($p<0.001$) and 18% ($p=0.047$) for the DE 110 and DE 150, respectively. The relative reductions of hemorrhagic stroke and ICH compared to warfarin ranged from 59% to 74%, with associated p-values of <0.0001.

The profound reductions in hemorrhagic stroke and intracranial hemorrhage with dabigatran compared to warfarin are arguably the most clinically important results in RE-LY. Although relatively uncommon, these events are the most feared complications of anticoagulant therapy. The fatality rates range from 50% for intracerebral bleeds (hemorrhagic strokes, [R09-1532]) to 25% for subdural and subarachnoid bleeds. Their socioeconomic cost and medical care costs are high and they are one of the most important factors in the

underutilization of anticoagulation in eligible patients. The risk of ICH with warfarin in RE-LY is 0.72%/year and the rate of hemorrhagic stroke is 0.38%/year. These rates are not dissimilar to rates observed in previous trials with warfarin (Figure 2.5.5.1.4: 1). Rates of ICH on warfarin in the ATRIA study, a cohort study of over 13,000 US AF patients were in the range of 0.4%/year but were 0.8%/year in patients at least 80 years old on warfarin [R09-1531]. A more recent analysis of the same database estimated rates of warfarin associated ICH to be 0.61%/year for patients with $CHADS_2$ score of 2, the median score in the RE-LY study (Singer et al, R09-4831). A Factor Xa inhibitor, idraparinux, investigated in this indication had rates of ICH that were more than double those seen with warfarin (AMADEUS, [P08-01644]).

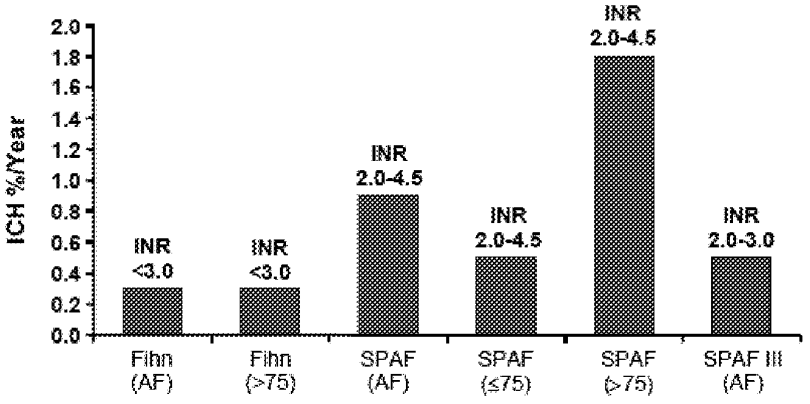


Figure 2.5.5.1.4: 1 Intracranial hemorrhage during long-term anticoagulation with warfarin

Age group cut off; less than or equal to 75 years and greater than 75 years
ICH = Intracranial hemorrhage, AF = Atrial fibrillation, INR= international normalized ratio, SPAF = Stroke Prevention in Atrial Fibrillation Investigators
Source data: Adapted from Levine et al 2004 [P04-10723]

The rate of ICH and hemorrhagic stroke with warfarin is strongly dependent on the age of the subjects and INR control (Fang et al., [R04-4519]; Singer et al., [R09-4831]). Therefore, we analysed the ICH and hemorrhagic stroke rates in RE-LY according to the level of INR control, using 60%, 65% and 67% (median) as the cutoffs. The results were similar for all cutoffs. We confirmed that the ICH and hemorrhagic stroke rates are higher on poorly controlled warfarin (<65% TTR) compared to well-controlled warfarin (≥ 65% TTR, [SCE Appendix 6, Table 2.1.1.2: 24]). However, the relative risk in the rate of ICH and hemorrhagic stroke with dabigatran compared to warfarin persisted also in comparison with warfarin subjects who had better INR control (for ICH: RR, DE110 vs. warfarin=0.29, 95% CI 0.17 to 0.50; RR DE150 vs. warfarin=0.36, 95% CI 0.22 to 0.60. [SCE Appendix 6, Table 2.1.1.2.22] For hemorrhagic stroke: RR DE110 vs. warfarin=0.26, 95% CI 0.12 to 0.58; RR DE150 vs. warfarin=0.21, 95% CI 0.09 to 0.49). [SCE Appendix 6, Table 2.1.1.2.20]. Thus the benefits of dabigatran compared to warfarin on these outcomes are not due to warfarin INR control as assessed by TTR or to an identifiable subgroup of warfarin subjects.

The observation of large reductions in both bleeding categories with both doses of (blinded) dabigatran compared to warfarin, across different levels of INR control, provides substantial, consistent, and reliable evidence of the impact of dabigatran on these major clinical events.

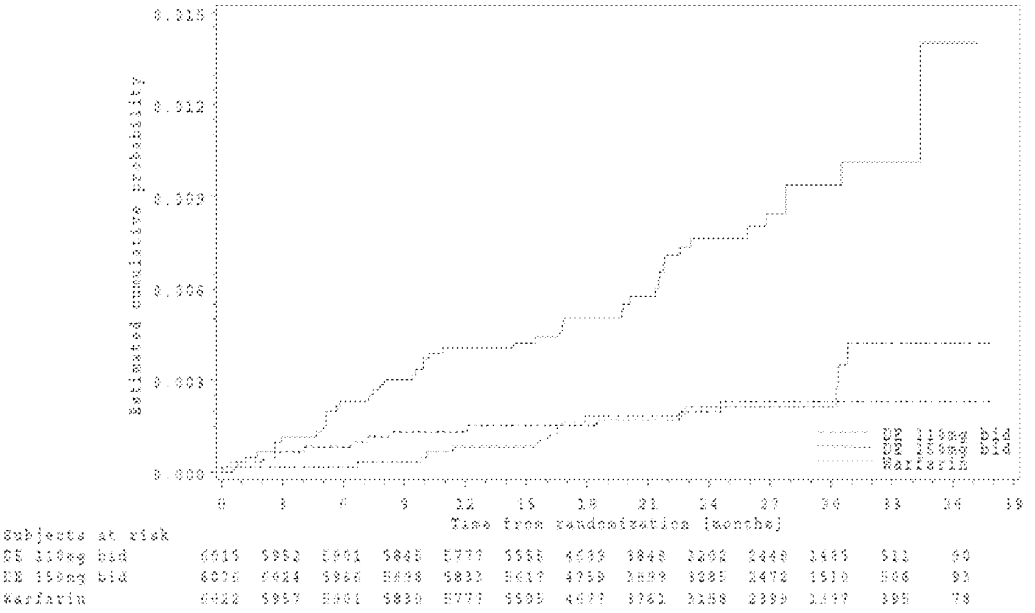


Figure 2.5.5.1.4: 2 Kaplan-Meier estimates of time to first hemorrhagic stroke in Study 1160.26

Source data: SCE Appendix 6, Figure 2.1.1.1.14

2.5.5.1.5 Minor and any (minor+major) bleeding events

Both minor bleeding events (investigator-reported) and any bleeding (minor+major) occurred less frequently in dabigatran subjects compared to warfarin subjects (Table 2.5.5.1.5: 1). The reduction with both dabigatran doses was statistically significant for any bleeds (DE 110 vs. warfarin, $p<0.001$, DE 150 vs. warfarin, $p=0.003$). Minor bleed rates were not analysed using Kaplan Meier, time-to-first-event methods since minor bleeds occurred multiple times in the same subject.

Table 2.5.5.1.5: 1 Yearly event rate of minor bleeding events in Study 1160.26 (randomized set)

	DE 110 mg bid N (%)	DE 150 mg bid N (%)	Warfarin N (%)
Investigator-reported bleeds			
Minor bleeds	1566 (13.16)	1787 (14.84)	1930 (16.36)
Any bleeds	1749 (14.70)	1990 (16.53)	2152 (18.24)

In case of recurrent event of the same category, the first event was considered. Minor bleeds were not adjudicated.
Subject-years = sum (date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: SCS Appendix 7, Table 2.1.1.1.1.6

2.5.5.1.6 Comparative bleeding rates, DE 110 versus DE 150

The two doses of dabigatran differed in their effects on bleeding. The low dose had significantly less major bleeding than the high dose (2.67%/year for DE 110 versus 3.11%/year for DE 150, RR 0.85, 95%CI 0.73-0.99, p=0.0356) as well as less 'any bleeding' (major+minor) than the high dose(DE 110 vs. DE 150, RR 0.86, 95%CI 0.81-0.92, p< 0.0001).

2.5.5.1.7 Gastrointestinal Bleeding

Dabigatran treatment resulted in a higher number bleeding events in the gastrointestinal system (GI) compared with warfarin. For major bleeds, the high dose of dabigatran increased the risk of GI bleeds compared to warfarin, by ~50% (p=0.0004, SCS Appendix 7, Table 2.1.1.1.1: 52). However, both doses increased the risk of minor GI bleeds by ~40 to 50% (Table 2.5.5.1.7: 1, p<0.0001 both doses versus warfarin).

The explanation for the increased GI bleed rate on dabigatran is not immediately clear. An exploratory analysis of the frequency of GI bleeds in subjects with GI adverse events showed that the adverse event of 'gastritis-like symptoms' but not dyspepsia was associated with a 2-3 fold higher rate of GI bleed regardless of treatment. The incidence of gastritis-like symptoms was approximately 4-5% on dabigatran and 2.4% on warfarin. The concomitant use of ASA increases the risk of GI bleed but only appears to be additive, not synergistic [SCS Appendix 7, Tables 2.1.1.2.3.1-5, SCS Appendix 7, Figures 2.1.1.2.3.6-7].

Table 2.5.5.1.7: 1 Frequency and yearly event rate of gastrointestinal bleeding events in study 1160.26 (randomized set)

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Number of subjects	6015	6076	6022
GI Major bleeds	132 (1.12)	181 (1.53)	118 (1.01)
GI Life threatening MBEs	67 (0.57)	91 (0.76)	56 (0.48)
Any GI bleeds[a]	600 (5.41)	680 (6.11)	449 (3.99)

* In case of recurrent event, the first event was considered
For subjects with event, subject-years= (first onset date - date of randomization + 1) / 365.25
For subjects without event, subject-years= (study termination date - date of randomization + 1)/365.25
Yearly event rate (%) = # of subjects with event / subject-years * 100.
[a] Any GI bleeds included adjudicated major GI bleeds and non-adjudicated minor GI bleeds.
Source data: SCS Appendix 7, Table 2.1.1.1.1.48

2.5.5.1.8 Discontinuations due to bleeding events

The number of subjects with permanent treatment discontinuation due to major bleeds was similar for all treatments, in the range of 1%. For minor bleeds, the number of subjects who permanently discontinued treatment was slightly higher for dabigatran (1.1% and 1.3% for DE 110 and DE 150, respectively) compared to warfarin (0.6%) (1160.26 [U09-3249-01], Table 15.1.1: 3). The higher rate of discontinuations for minor bleeds may be a consequence of the open-label nature of the study, with a lower threshold for discontinuing an experimental drug.

2.5.5.1.9 Recurrent bleeding events

There were fewer dabigatran subjects with major bleeding events compared to warfarin. Most of the subjects (85%) who had a major bleeding event during the study had only one event (Table 2.5.5.1.9: 1). The proportions of subjects with two events was approximately the same across treatments (11-12%) but there were less subjects with three or more major bleeds on warfarin, 1%, versus 4-5% on dabigatran. For any bleeds, which is the sum of minor+major bleeds, there were fewer dabigatran subjects with bleeding events. Approximately 57-60% of the subjects who had any bleeding event during the study had only one bleeding event. Multiple bleeding events were more frequent on warfarin than on dabigatran. It is difficult to interpret the significance of the differences in multiple bleeds.

The primary method of analysis for bleeding in this study was a Kaplan-Meier survival analysis of the time to first event, with annualized event rates estimated based on this calculation. Treatment differences were assessed by comparisons of the hazard ratios. The frequency of recurrent major bleeding was small and generally substantiated the observed treatment differences based on time to first event. Similarly, the pattern of multiple any bleeding, which is largely driven by minor bleeds, also substantiated the Kaplan Meier analysis.

Table 2.5.5.1.9: 1 Subjects with bleeding events during the study by the number of occurrences in Study 1160.26 (randomized set)

	DE 110	DE 150	Warfarin	Total
Total randomized	6015	6076	6022	18113
Adjudicated Major bleeds				
Total with event	318	375	396	1089
Total number of major bleeds	380	460	455	1295
Number of occurrences				
1	269	314	344	927
2	36	43	48	127
>= 3	13	18	4	35
Investigator-reported any bleeds[a]				
Total with event	1749	1990	2152	5891
Total number of any bleeds	3001	3652	3951	10604
Number of occurrences				
1	1046	1132	1263	3441
2	412	456	475	1343
3	151	196	218	565
4	80	116	94	290
>= 5	60	90	102	252

[a] Includes adjudicated major bleeds and non-adjudicated minor bleeds.
Source data: SCS Appendix 7, Tables 2.1.1.1.1.56 and 2.1.1.1.1.57

2.5.5.1.10 Bleeding: subgroup analyses by baseline demographics

Bleeding rates were analysed by subgroup to determine if there were important differences due to demographics, concomitant diseases or concomitant drugs.

Age was the only demographic variable with a significant treatment interaction ($p<0.0001$) in Trial 1160.26 (SCS Appendix 7, Table 2.1.1.1.1.28). The greater the age of the subject, the higher the yearly event rate for major bleeds. For subjects <75 years of age, DE 110 bid and DE 150 bid had a lower rate of major bleeds compared to warfarin; however, DE 150 bid subjects ≥75 years of age had a slightly higher rate of major bleeds compared to warfarin (SCS Appendix 7, Table 2.1.1.1.1.24). SCS Appendix 7, Figures 2.1.1.1.1.26 and 2.1.1.1.1.27 illustrate the effects of demographics on risk of major bleeds for the three treatment groups (Figures 2.5.5.1.10: 1 and 2.5.5.1.10: 2).

Renal dysfunction was associated with a high risk of bleeding for all treatments. In subjects with moderate renal dysfunction (CrCl 30-50 mL/min), bleeding rates for DE 110 bid and DE 150 bid were comparable to warfarin. For subjects in which CrCl >50 mL/min, major bleed rates were lower for both DE 110 bid and DE 150 bid subjects compared to warfarin. There were too few subjects with CrCl <30 mL/min to draw conclusions.

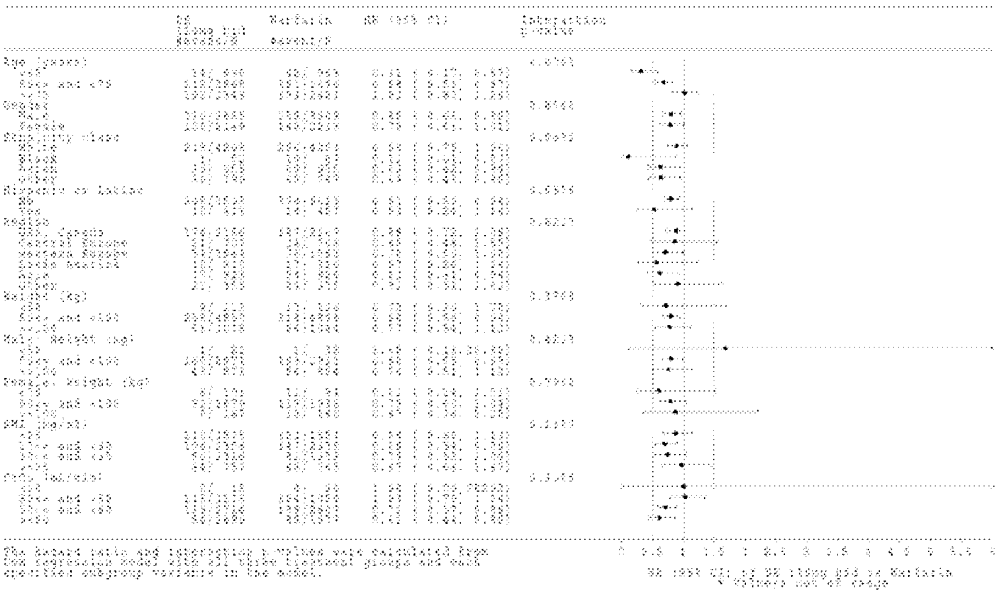


Figure 2.5.5.1.10: 1 Hazard ratio and 95% CI for major bleeds comparing DE 110 bid to warfarin by baseline demographics in study 1160.26 (randomized set)

Source data: SCS Appendix 7, Figure 2.1.1.1.1.26

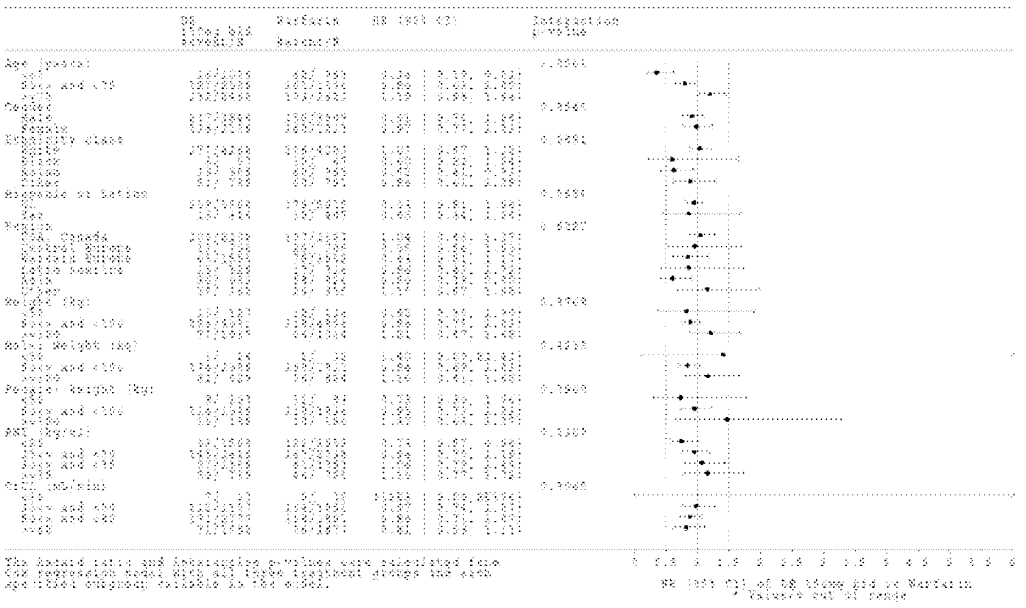


Figure 2.5.5.1.10: 2 Hazard ratio and 95% CI for major bleeds comparing DE 150 bid to warfarin by baseline demographics in study 1160.26 (randomized set)

Source data: SCS Appendix 7, Figure 2.1.1.1.1.27

To clarify whether there were interactions among the possible risk factors for major bleeding, a Cox proportional model was used to compare the major bleed rates on dabigatran and warfarin in the presence of important covariates: age at entry (years), CrCL at entry (mL/min), gender and ASA use during study, and all two-factor interaction terms (SCS Appendix 7, Table 2.1.1.1.7.3). Baseline age and CrCL are considered as continuous covariates.

The effects of renal function on bleed rates were either minor or undetectable when age was taken into account. Figure 2.5.5.1.10: 3 shows that hazard ratio of major bleed for dabigatran 150mg bid vs warfarin is almost the same regardless of the different CrCL values explored. For dabigatran 110mg bid vs. warfarin, there is some effect of the lower baseline CrCL value (40 mL/min). However, in general the most important consideration in relative bleeding risk is age.

As can be seen from the figure, for DE 110 the relative risk compared to warfarin exceeds 1.0 only above the age of ~85 years. For DE 150, the risk exceeds 1.0 above the age of ~75 years.

2.5 CLINICAL OVERVIEW

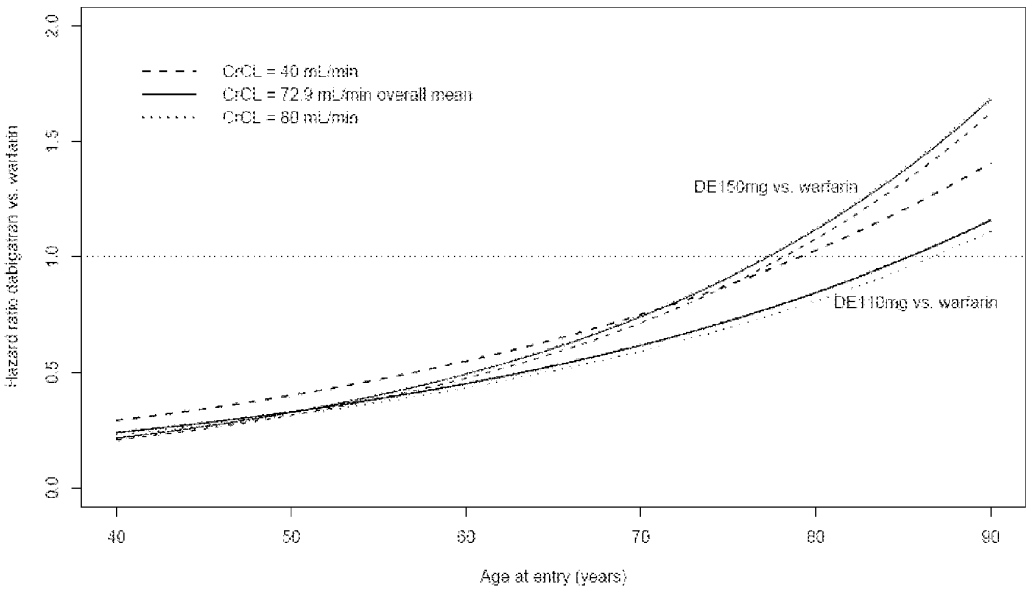


Figure 2.5.5.1.10: 3 Hazard ratio of major bleed (dabigatran vs. warfarin) by continuous age at selected CrCL values (randomized set)

Source data: SCS Appendix 7, Table 2.1.1.1.7.3

Decreasing renal function is associated with decreasing advantages of dabigatran over warfarin in the rate of major bleeding (Figure 2.5.5.1.10: 4, left panel). However, when age is included in the model the effect is no longer relevant (SCS Appendix 7, Table 2.1.1.1.7.3). This is more obvious in the DE 150 vs. warfarin comparison, for which the treatment by CrCL interaction is negligible (shown as an almost flat curve in Figure 2.5.5.1.10: 4, the right panel). For the DE 110 vs. warfarin comparison, the treatment by CrCL interaction is marginally significant (p-value = 0.165, Figure 2.5.5.1.10: 4, right panel).

ASA use during study has a strong effect on bleeding risk. Subjects who took ASA at least once during the study almost doubles the risk of major bleed (hazard ratio = 1.91, p-value<0.001) comparing with those who did not use ASA during the study. However, ASA use does not interact with treatment, i.e. there is no difference of the ASA effect across dabigatran doses or warfarin.

Gender is marginally significant: male subjects had a slightly higher risk of major bleed than female subjects (hazard ratio = 1.21, p-value = 0.079). However, gender does not interact with treatment effect.

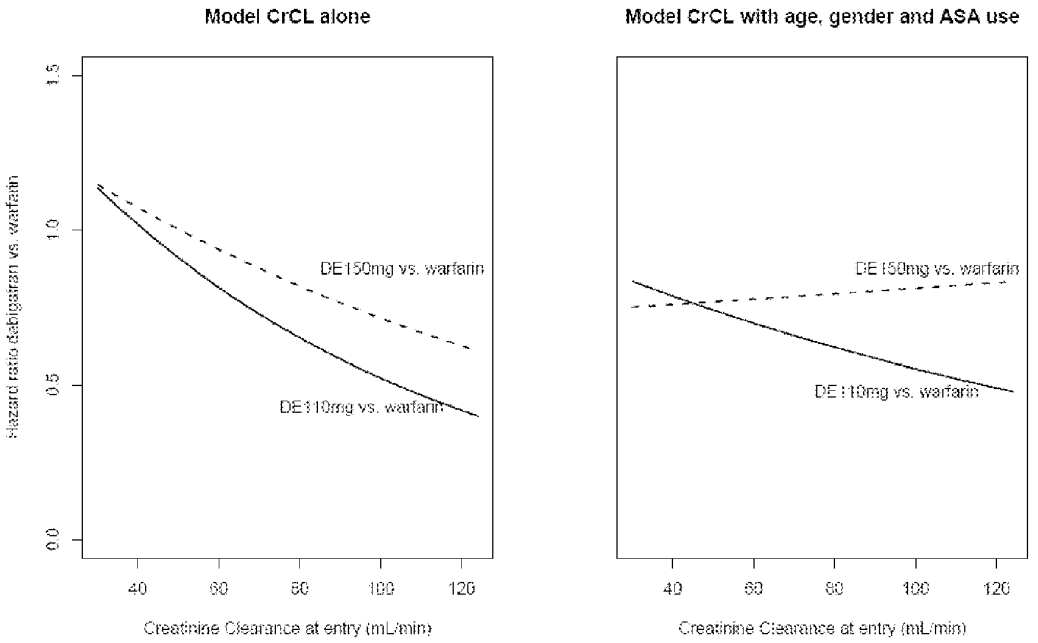


Figure 2.5.5.1.10: 4 Hazard ratio of major bleed (dabigatran vs. warfarin) by continuous CrCL values with parameters estimated from two models: on the left from the model with treatment and treatment by CrCL interaction only; on the right, from the model with age, CrCL, gender, ASA use during study, and all two-factor interaction terms. (randomized set)

Source data: SCS Appendix 7, Table 2.1.1.1.7.2 and Table 2.1.1.1.7.3

2.5.5.1.11 Bleeding events by stroke risk factors

The frequencies of major bleeding events by baseline stroke risk factors, $CHADS_2$ score and type of atrial fibrillation in Trial 1160.26 are shown in (SCS Appendix 7, Tables 2.1.1.1.1.41 and 35 and 1160.26 [U09-3249-01] Tables 15.3.2.2.4: 5 and 6), respecively.

The protocol specified stroke risk factors also predicted an increased risk of major bleeding in this study. There were several significant treatment-by-risk-factor interactions (SCS Appendix 7, Figure 2.1.1.1.1.37 and 38). For DE 110 bid however, the hazard ratios were generally less than 1.00, i.e there were less major bleeds for DE 110 bid than for warfarin. For DE 150 bid the hazard ratios compared to warfarin were greater than 1.00 in the risk factor groups for age≥75 and age≥65 with diabetes.

Bleeding subgrouped by $CHADS_2$ scores

The annualized rate of major bleeds increased with the number of risk factors (higher $CHADS_2$ score) for all treatment groups. Subjects treated with DE 110 bid had the lowest rate of major bleeds across all $CHADS_2$ scores. For subjects treated with DE 150 bid, the hazard

ratio compared to warfarin was less than 1 for all categories except for a $CHADS_2$ score of 3 or higher (hazard ratio 1.1, [SCS Appendix 7, Table 2.1.1.1.1.43].

Table 2.5.5.1.11: 1 Yearly event rate of major bleeds by baseline CHADS2 score in study 1160.26 (randomized set)

	DE 110 bid		DE 150 bid		Warfarin	
CHADS2 Score	# of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)	# of subjects	Yearly event rate (%)
0	151	1.59	146	1.00	155	2.16
1	1809	1.83	1815	2.04	1707	2.75
2	2088	2.64	2136	2.80	2229	3.14
3+	1966	3.60	1979	4.64	1931	4.26

In case of recurrent event, the first event was considered.
Subject-years = sum (date of study termination - date of randomization + 1) of all randomized subjects / 365.25; Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: SCS Appendix 7, Table 2.1.1.1.1.41

2.5.5.1.12 Bleeding risk and concomitant medications

The annualized rates of major and minor bleeds by concomitant medication use were evaluated for medications of interest, specifically antiplatelets and NSAIDs, P-glycoprotein inhibitors (quinidine, diltiazem, verapamil, and amiodarone), and drugs that reduce gastric acid (proton pump inhibitors, H2-blockers) which might reduce absorption of study medication. (Table 2.5.5.1.12: 1 and [SCS Appendix 7, Table 2.1.1.1.1.31].

The use of ASA nearly doubled the rate of major bleeds, regardless of treatment (yearly rate with vs. without ASA, respectively, was 1.98% vs.3.74% for DE 110 bid; 2.23% vs. 4.51% for DE 150 bid; and 2.44% vs. 4.77% for warfarin). The concomitant use of clopidogrel, ASA+clopidogrel, COX2 inhibitors, other NSAIDs, and oral anticoagulants also increased the rate of major bleeds for all subjects, regardless of treatment. Since the use of these agents was not randomized, the subjects who used them may be demographically different from the subjects who did not.

The calcium channel blockers diltiazem and verapamil were associated with increased rates of major bleeding in all treatment groups. However, their use was not randomized and may be associated with subjects with different risk factors compared to those who do not take these drugs. If there is a P-gp effect it would be reflected in a change in the relative risk versus warfarin, which is not a P-gp substrate. The relative risk of bleeding for dabigatran versus warfarin did not increase with the possible exception of verapamil co-administration with DE 150 bid treatment. However, this increased relative risk was not observed when any bleeds were evaluated. Thus, there is no consistent evidence of an increased bleeding risk with verapamil.

For amiodarone, another P-gp inhibitor, there was no evidence of an increased risk of bleeding relative to warfarin. For quinidine, there were very few subjects but there was no indication of an increased bleeding risk.

The use of both proton pump inhibitors and H2-blockers was associated with higher bleeding rates for all treatments. There was no relevant difference in relative risk of bleeding for

dabigatran versus warfarin associated with the use of these drugs. Since PPIs and H2-blockers may decrease plasma concentrations of dabigatran, the bleed risk should decrease. No such effect was seen.

Table 2.5.5.1.12: 1 Yearly event rate of major bleeding events by concomitant medication use in study 1160.26 (randomized set)

% of time taking concomitant medication	DE 110 bid # of subjects	DE 110 bid Subjects with event	DE 110 bid Yearly event rate (%)	DE 150 bid # of subjects	DE 150 bid Subjects with event	DE 150 bid Yearly event rate (%)	Warfarin # of subjects	Warfarin Subjects with event	Warfarin Yearly event rate (%)
Antithrombotic therapy									
ASA									
0% (never)	3615	143	1.98	3687	164	2.23	3615	175	2.44
Used at least one time	2400	175	3.74	2389	211	4.51	2407	221	4.77
Clopidogrel									
0% (never)	5571	272	2.46	5624	325	2.92	5581	342	3.13
Used at least one time	444	46	5.38	452	50	5.41	441	54	6.25
Oral anticoagulant									
0% (never)	5282	231	2.22	5323	282	2.68	5417	312	2.95
Used at least one time	733	87	5.90	753	93	6.08	605	84	6.89
ASA+Clopidogrel									
0% (never)	5708	283	2.50	5779	343	3.00	5717	359	3.21
Used at least one time	307	35	5.90	297	32	5.37	305	37	6.12
Anti hypertensive									
ACE inhibitors									
0% (never)	2997	144	2.42	3033	174	2.89	3032	202	3.42
Used at least one time	3018	174	2.92	3043	201	3.34	2990	194	3.30
Beta blockers, calcium channel blockers and drugs used in AF									
Calcium channel blockers									
Verapamil									
0% (never)	5589	291	2.64	5654	340	3.04	5565	364	3.35
Used at least one time	426	27	3.14	422	35	4.07	457	32	3.46
Diltiazem									
0% (never)	5312	252	2.41	5367	309	2.92	5302	330	3.19
Used at least one time	703	66	4.60	709	66	4.50	720	66	4.54
Amiodarone									
0% (never)	5134	253	2.49	5177	312	3.04	5100	321	3.20
Used at least one time	881	65	3.76	899	63	3.57	922	75	4.21
Quinidine									
0% (never)	5974	317	2.68	6036	372	3.11	5979	395	3.37
Used at least one time	41	1	1.30	40	3	3.27	43	1	1.08
Metabolic and anti inflammatory									
COX2 inhibitor									
0% (never)	5857	302	2.61	5912	358	3.06	5858	376	3.28
Used at least one time	158	16	4.61	164	17	4.92	164	20	6.00
Other NSAID									
0% (never)	5231	256	2.48	5350	312	2.96	5253	324	3.15
Used at least one time	784	62	3.92	726	63	4.24	769	72	4.74
Other drugs									
Proton pump inhibitors									
0% (never)	4535	176	1.96	4575	176	1.93	4752	229	2.46
Used at least one time	1480	142	4.89	1501	199	6.80	1270	167	6.73
H2 blockers									
0% (never)	5543	257	2.34	5596	313	2.82	5562	332	3.05
Used at least one time	472	61	6.63	480	62	6.60	460	64	7.15

In case of recurrent event, the first event was considered. Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25.Yearly event rate (%) = # of subjects with event / subject-years * 100
Source data: SCS Appendix 7, Table 2.1.1.1.1.31

2.5.5.1.13 Major bleeds versus subgroups of INR control

When warfarin is well controlled (INR time in therapeutic range 2-3 ≥65%) it is associated with an approximately one third lower rate of major bleeds than in subjects with poor control (TTR <65%, Table 2.5.5.1.13: 1). Compared to poorly controlled warfarin, all dabigatran bleed rates were lower. Compared to well-controlled warfarin the rate of major bleeding was slightly higher for the DE 150 group. However, the rates of ICH and hemorrhagic stroke were still significantly lower than in this post hoc selection of warfarin subjects.

Table 2.5.5.1.13: 1 Yearly event rate for major bleeds by INR control in Study 1160.26 (safety set)

INR Range for Warfarin:	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
INR in range 2-3 >=65% of the time			
Number of subjects	5984	6059	3170
Subject-years	10229	10253	6133
Major bleeds	275 (2.69)	329 (3.21)	168 (2.74)
Life threatening MBEs	117 (1.14)	136 (1.33)	84 (1.37)
Other MBEs	173 (1.69)	207 (2.02)	88 (1.43)
ICH	19 (0.19)	24 (0.23)	39 (0.64)
INR in range 2-3 <65% of the time			
Number of subjects	5984	6059	2619
Subject-years	10229	10253	4489
Major bleeds	275 (2.69)	329 (3.21)	179 (3.99)
Life threatening MBEs	117 (1.14)	136 (1.33)	91 (2.03)
Other MBEs	173 (1.69)	207 (2.02)	97 (2.16)
ICH	19 (0.19)	24 (0.23)	37 (0.82)

*In case of recurrent event, the first event was considered
Subject-years = sum(date of last drug intake - date of first drug intake + 1) of all treated subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.
Source data: 1160.26 [U09-3249-01], Tables 15.3.2.1: 13 and 15.3.2.1: 15

2.5.5.1.14 Major bleeding events by prior Vitamin K antagonist use

The yearly event rate of a major bleeding event was generally similar within treatment groups for VKA naïve and VKA experienced subjects, although VKA experienced subjects treated with DE 110 had a slightly lower yearly rate of major bleeds compared to VKA naïve subjects (2.81% vs. 2.55%, respectively) (SCS Appendix 7, Table 2.1.1.1.1.17).

2.5.5.2 OTHER ADVERSE EVENTS

Phase II exposure in AF was limited to two trials with 12 weeks treatment duration and 676 subjects, and one rollover trial of 361 of these subjects treated for up to 5 years. The total

exposure was less than 2,000 subject-years. In general the pattern of adverse events did not differ from those observed in the large Phase III trial, 1160.26, with over 30,000 subject-years of exposure. Therefore the adverse event results of the Phase II trials (1160.20, 1160.42, and 1160.49) are briefly summarized here and the primary analysis of long-term safety is based on the Phase III trial.

Trial 1160.20 (PETRO, [U06-1615-02])

A dose response was observed for dabigatran for GI discomfort/pain (abdominal discomfort, abdominal pain, dyspepsia, gastritis, oesophageal pain). Dyspepsia was most frequently observed at higher doses of dabigatran, whereas no dyspepsia was reported for warfarin.

- There were no deaths during the study period, but one subject died 40 days after trial participation.
- SAEs were reported for 8.2% subjects. Approximately 6% of subjects discontinued from the study due to one or more AEs.

Trial 1160.42 PETRO-EX, was an extension of 1160.20 (1160.42 [U09-3247-01]) and included only dabigatran treatment:

- Gastrointestinal AEs were most frequently reported, including nausea, dyspepsia, diarrhoea, constipation, upper abdominal pain. Nervous system disorders were dizziness and headache. There was no apparent dose relationship.
- Discontinuation of study medication due to AEs occurred in approximately one-third of subjects.
- SAEs occurred in approximately half the subjects participating in this trial.

Trial 1160.49 (1160.49 [U07-3126]):

- AEs, except for bleeding events and abdominal pain/dyspepsia, were not dose-dependent in the dabigatran dose groups.
- The number of subjects who discontinued from the study due to bleeding events was similar among the three dose groups.
- No SAEs related to the investigational drug occurred in the dabigatran groups.

2.5.5.2.1 Other common AEs in RE-LY

In Trial, 1160.26, other AEs were summarized for a total of 18,042 subjects in the safety set. Summaries of AEs include treatment-emergent AEs, defined as AEs that occurred from the time of the first dose of study drug up to six days following the last dose of study drug. Since the outcome events in this trial (stroke, SEE, death, MI, PE, TIA, bleeds) were analyzed as efficacy or safety endpoints, they were not summarized as AEs unless they were considered related to study medication by the investigator. Each subject was counted once for each particular AE, regardless of the number of times an AE was reported.

Overview of other AEs in Trial 1160.26

The incidence of AEs was similar for the two dabigatran doses (78.6% and 78.3% for DE 110 and DE 150, respectively). The incidence on warfarin was slightly lower at 75.9%. Dabigatran subjects had a higher incidence of AEs leading to treatment discontinuation (Table 2.5.5.2.1: 1). The incidence of SAEs was similar across treatment groups. Dabigatran subjects, however, had a lower incidence of fatal AEs, life-threatening AEs, and events that required hospitalization compared to warfarin subjects.

Table 2.5.5.2.1: 1 Overview of other AEs in Study 1160.26 (safety set)

	DE 110 bid N (%)	DE 150 bid N (%)	Warfarin N (%)
Number of subjects	5984 (100.0)	6059 (100.0)	5999 (100.0)
Subjects with any AE	4706 (78.6)	4745 (78.3)	4552 (75.9)
Subjects with severe AEs	1726 (28.8)	1749 (28.9)	1705 (28.4)
Subjects with investigator defined drug-related AEs	1243 (20.8)	1332 (22.0)	949 (15.8)
Subjects with other significant AEs (according to ICH E3)	773 (12.9)	873 (14.4)	582 (9.7)
Subjects with AEs leading to discontinuation of trial drug	1138 (19.0)	1241 (20.5)	935 (15.6)
Subjects with SAEs	1266 (21.2)	1291 (21.3)	1356 (22.6)
Fatal	108 (1.8)	100 (1.7)	120 (2.0)
Immediately life-threatening	50 (0.8)	46 (0.8)	64 (1.1)
Disability/incapacitating	576 (9.6)	533 (8.8)	592 (9.9)
Required hospitalization	1076 (18.0)	1091 (18.0)	1178 (19.6)
Prolonged hospitalization	95 (1.6)	71 (1.2)	89 (1.5)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)
Other	214 (3.6)	251 (4.1)	230 (3.8)

A subject may be counted in more than one seriousness criterion.
Percentages are calculated using total number of subjects per treatment as the denominator.
MeDRA version used for reporting: 12.0
Source data: SCS Appendix 7, Table 2.1.1.2.1.1

The System Organ Classes with the highest incidence of AEs for dabigatran and warfarin subjects were GI Disorders, Infections and Infestations, and General Disorders. Dabigatran subjects had the highest incidence of gastrointestinal AEs (34.6%, 34.5%, and 24.1% for DE 110 bid, DE 150 bid, and warfarin, respectively). Diarrhea, dyspepsia, and nausea were the most frequently reported GI AEs, all of which were reported at a higher frequency with DE 110 bid and DE 150 bid treatment, particularly for dyspepsia and related preferred terms. Dyspepsia and gastritis as AEs are discussed in further detail below.

The most frequently occurring AEs for DE 110 bid, DE 150 bid, and warfarin subjects were dyspnea (8.3%, 8.7%, and 9.2%, respectively), dizziness (7.6%, 7.6%, and 9.3%), and peripheral edema (7.5%, 7.3%, and 7.6%). For these events, the highest incidence was in warfarin subjects. Adverse events occurring with at least a 5% frequency in any treatment group are displayed in Table 2.5.5.2.1: 2.

Table 2.5.5.2.1: 2 AEs with a frequency >5% in Study 1160.26 [N (%)] (safety set)

Adverse Event	DE110 BID	DE150 BID	Warfarin
Dyspepsia*	762 (12.7)	738 (12.2)	354 (5.9)
Dizziness	457 (7.6)	458 (7.6)	555 (9.3)
Dyspnoea	497 (8.3)	525 (8.7)	550 (9.2)
Oedema peripheral	446 (7.5)	442 (7.3)	453 (7.6)
Fatigue	370 (6.2)	367 (6.1)	353 (5.9)
Cough	319 (5.3)	310 (5.1)	345 (5.8)
Chest pain	288 (4.8)	355 (5.9)	342 (5.7)
Back pain	295 (4.9)	289 (4.8)	331 (5.5)
Arthralgia	249 (4.2)	313 (5.2)	328 (5.5)
Nasopharyngitis	314 (5.2)	309 (5.1)	327 (5.5)
Diarrhoea	355 (5.9)	367 (6.1)	327 (5.5)
Atrial fibrillation	303 (5.1)	313 (5.2)	326 (5.4)
Urinary tract infection	242 (4.0)	253 (4.2)	315 (5.3)
Upper respiratory tract infection	266 (4.4)	261 (4.3)	297 (5.0)

*includes dyspepsia, abdominal pain upper, abdominal pain, abdominal discomfort, epigastric discomfort
Percentages are calculated using total number of subjects per treatment as the denominator
Source data: SCS Appendix 7, Table 2.1.1.2.1.11

Subjects treated with DE 150 bid had a higher incidence of anemia compared with subjects treated with warfarin (3.0%, 3.4%, and 2.7% for DE 110 bid, DE 150 bid, and warfarin, respectively). This finding is consistent with the the higher frequency of hemoglobin decreases associated with major bleeding in the dabigatran treatment groups (see table on major bleed criteria, [SCS Appendix 7, Table 2.1.1.1.1.7]). A tabulation of all AEs in trial 1160.26 with a frequency >1% is shown in SCS Appendix 7, Table 2.1.1.2.1.2.

Thrombocytopenia occurred in 0.6%, 0.4% and 0.5% of subjects on DE 110, DE 150, and warfarin, respectively. These events were likely associated with bleeding.

2.5.5.2.2 Dyspepsia and gastritis

Dyspepsia was reported more frequently for DE 110 and DE 150 subjects compared with warfarin (6.1%, 5.7%, and 1.4%, respectively). Gastritis was reported in 2.5%, 2.1%, and 1.5% of DE 110, DE 150, and warfarin subjects, respectively (SCS Appendix 7, Table 2.1.1.2.3.1). A Kaplan-Meier analysis shows that the increased risk for dyspepsia with dabigatran occurred within the first month or so. Thereafter, the incidence increased equally in all treatment groups (Figure 2.5.5.2.2: 1).

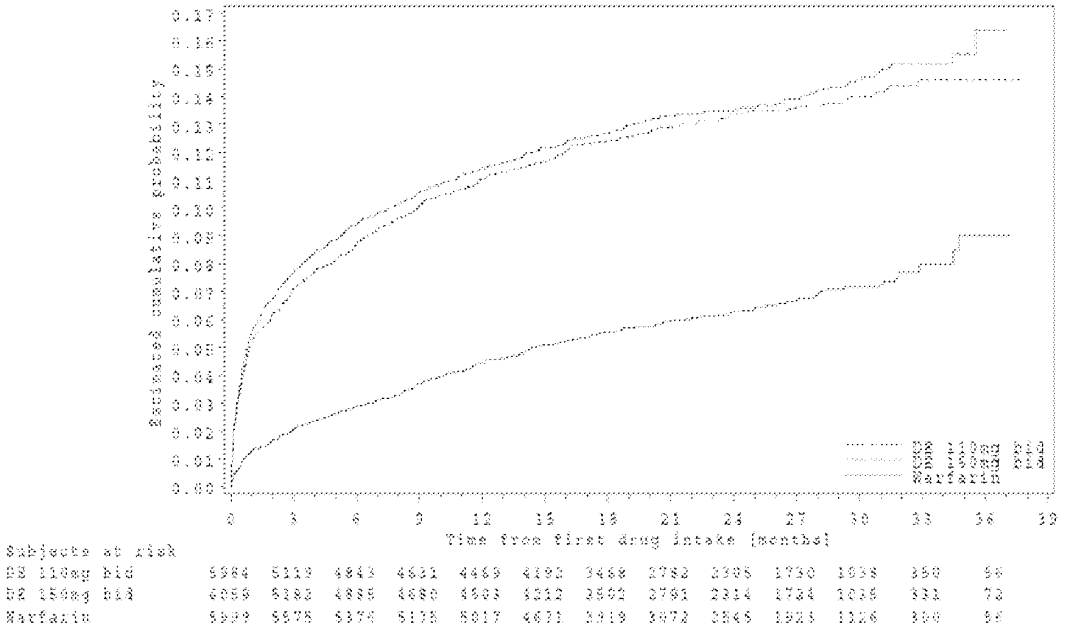


Figure 2.5.5.2.2: 1 Kaplan-Meier estimates of time to first dyspepsia in Study 1160.26 (safety set)

Source data: SCS Appendix 7, Figure 2.1.1.2.3.6

2.5.5.2.3 AEs leading to treatment discontinuation in RE-LY

In Trial 1160.26, a higher percentage of dabigatran subjects discontinued study medication due to AEs compared with warfarin subjects (19.0%, 20.5%, and 15.6% for DE 110 bid, DE 150 bid, and warfarin, respectively). AEs that resulted in discontinuation of treatment mirrored the types of SAEs that were reported most frequently in this study: cardiac disorders, infections and infestations, and GI disorders (SCS Appendix 7, Table 2.1.4.1.1).

Discontinuation of treatment due to GI disorders occurred more frequently in both dabigatran groups compared to warfarin, with dyspepsia resulting in discontinuation most often (1.0%, 0.9%, and 0.03% for DE 110 bid, DE 150 bid, and warfarin, respectively.

2.5.5.2.4 Adverse Events Leading to Death in RE-LY

In Trial 1160.26, all deaths were adjudicated for cause of death. Because outcome events, including death, were captured as adjudicated efficacy measures, some exemptions from expedited safety reporting were instituted. Deaths were only reported as SAEs when they were considered related to study treatment by the investigator. Of the 1372 deaths that occurred during the trial, 365 subjects had an adverse event with a fatal outcome identified by a study investigator.

The incidence of fatal AEs was 2.0%, 1.8%, and 2.2% for DE 110 bid, DE 150 bid, and warfarin, respectively.

The SOCs with the highest percentage of subjects with AEs leading to death were neoplasms, cardiac disorders, and infections and infestations; the incidence of AEs within each SOC was similar across treatment groups. Three warfarin subjects died of hepatic failure compared with one DE 110 bid subject; no DE 150 bid subjects died of hepatic failure.

2.5.5.3 NET CLINICAL BENEFIT ANALYSES IN STUDY 1160.26

The prespecified NCB endpoint included stroke, SEE, PE, MI, all cause death and major bleed. The risk reductions in NCB for DE 110 and DE 150 were 8% and 10%, respectively, with corresponding p-values of 0.100 and 0.0372 ([SCE Appendix 6, Table 2.1.1.6.2]). Therefore both dabigatran doses were more beneficial than warfarin.

For the prespecified NCB endpoint, the treatment effects of DE were consistent for all subgroups investigated. In a comparison of the two dabigatran doses for this endpoint, there was a significant interaction with $CHADS_2$ scores. For $CHADS_2$ scores of 3 or more DE 110 was more beneficial than DE150 (Figure 2.5.5.3: 1).

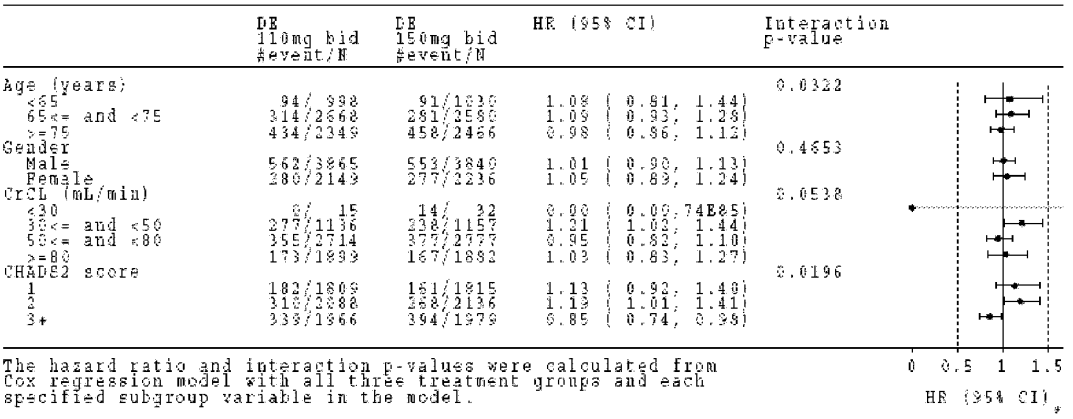


Figure 2.5.5.3: 1 Hazard ratio and 95% CI for Net Clinical Benefit comparing DE 110 bid and DE 150 bid

Source data: SCE Appendix 6, Figure 4.1.1.7.7

Composite of stroke/SEE and major bleeds

A composite endopoint of stroke/SEE or major bleed was evaluated as measure of benefit/risk. In the overall population, the risk of stroke/SEE or major bleed was reduced 13% and 12% for the DE 110 bid and DE 150 bid dose groups compared to warfarin (Hazard ratio of 0.87 and 0.88, respectively). This was statistically significant for the DE 110 bid group (p = 0.0297) but not for DE 150 bid (p = 0.0527) (SCE Appendix 6, Table 4.1.1.2.2).

Comparing doses of dabigatran, there was a significant interaction with age for the composite endpoint (SCE Appendix 6, Figure 4.1.1.2.6 and 4.1.1.2.7). For subjects < 65 years the high dose is clearly better. For subjects ≥ 75 years, the low dose appears slightly better than the high dose (relative risk 0.93).This most likely reflects the increase risk of bleeding in older subjects with the high dose, which is counterbalanced in part by the effectiveness of the high dose on stroke/SEE.

Stroke/vascular death/life threatening bleeds in Study 1160.26

The DE 150 dose had significant advantages over warfarin on the individual outcomes of stroke, vascular death and life-threatening bleeds. We compared the two dabigatran doses for important subgroups using a composite of these three outcomes. The high dose appears beneficial compared to DE 110 when the population was subgrouped by age, gender, renal function, and $CHADS_2$ score (SCE Appendix 6, Figure 4.1.1.8.7). Only with a $CHADS_2$ score ≥ 3 and age ≥ 75 was the net clinical benefit of high dose marginally less than that of DE 110, i.e., risk ratios < 1.0.

2.5.5.4 LIVER FUNCTION TEST ELEVATIONS IN THE SPAF II/III TRIALS

Sensitivity analyses for LFT elevations for all SPAF trials

Figure 2.5.5.4: 1 illustrates the cumulative incidence of ALT/AST elevations >3xULN associated with total bilirubin of >2xULN (potential Hy's Law cases) in all SPAF Phase II/III studies combined for dabigatran and warfarin groups. Dabigatran shows a lower risk of such elevations compared to warfarin.

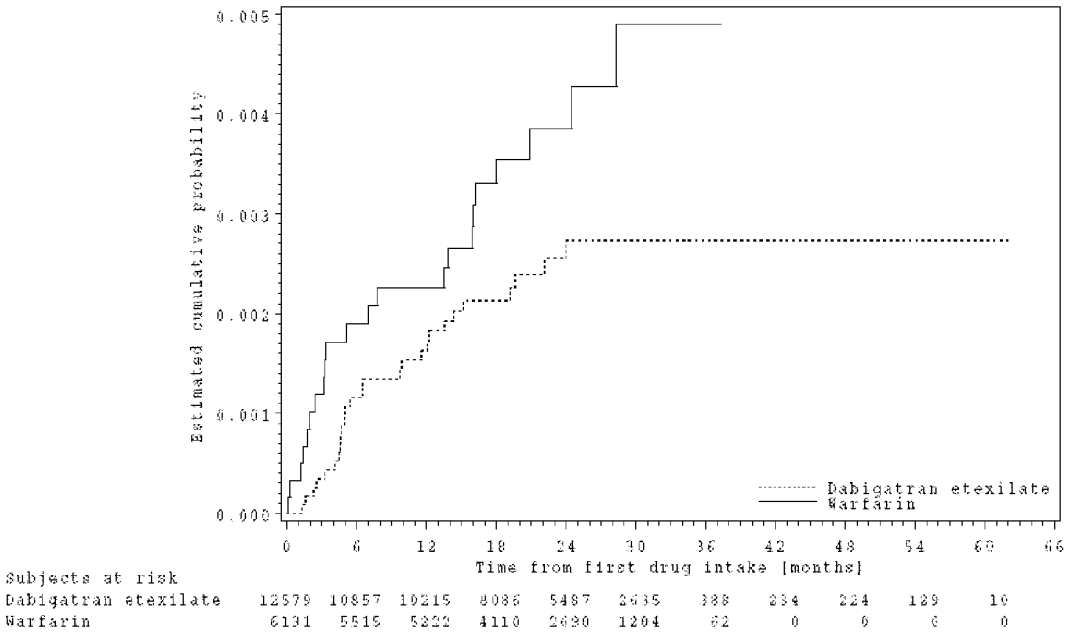


Figure 2.5.5.4: 1 Cumulative incidence of ALT/AST>3xULN and Bilirubin >2xULN in all SPAF Phase II/III studies combined (1160.20, 1160.49, 1160.42, and 1160.26)

Source: Module 5.3.5.3, Appendix 7, Figure 3.1.1.1

2.5.5.4.1 Liver function test elevations in trial 1160.26 (RE-LY)

Liver function was closely monitored during the RE-LY trial. LFTs were measured monthly in every subject during the first year of exposure and 4 monthly thereafter.

Transaminases >5xULN, or transaminase elevations >3xULN with concomitant bilirubin elevations >2xULN, so-called potential Hy's law cases, prompted immediate discontinuation of treatment and rigorous follow-up for a clinical cause. These transaminase elevations >3x ULN, associated with a bilirubin elevation >2x ULN in the next 30 days, were evaluated for biliary obstruction (e.g., based on alkaline phosphatase elevation) or other alternative clinical cause. Absent these alternative explanations, such cases were to be defined as actual Hy's Law cases, a particularly ominous event indicative of hepatic damage that leads to death or liver transplantation in 10% of cases [R02-1064].

After approximately 10,000 subjects had been recruited and over 6,000 subjects had been treated for at least 6 months, a pre-specified interim analysis of hepatic safety was performed by the Data Monitoring Committee. There was no indication of hepatotoxicity. This led to a decrease in the frequency of monitoring during the first year of exposure for all subjects, from monthly tests to tests only at regular trial visits (Months 1, 3, 6 and 12).

Table 2.5.5.4.1: 1 summarizes the complete 'on treatment' hepatic function tests (safety set), including occurrence of AST and ALT elevations and associated elevations in total bilirubin (within 30 days of AST/ALT elevation). The Kaplan-Meier curves for transaminases > 3xULN and potential Hy's Law cases (transaminases >3xULN with a rise in bilirubin >2xULN) are shown in Figures 2.5.5.4.1: 1 and 2.5.5.4.1: 2.

There was no evidence of increased frequencies on dabigatran compared to warfarin in transaminase elevations, or concomitant transaminase and bilirubin elevations. If anything, the abnormalities were more frequent on warfarin.

Transaminase elevations <2x ULN were common (27 to 31%) in this population. For transaminases >3xULN, the overall frequency was 1.8 to 2.1%. For potential Hy's Law cases, there were 11 subjects (0.2%) on D110, 14 subjects (0.2%) on D150 and 22 subjects (0.4%) on warfarin. All but 4 of these cases (2 dabigatran, 2 warfarin) had identifiable alternative causes. The most frequent reasons for the abnormalities were cholelithiasis, heart failure/cardiac shock, and cancer.

Table 2.5.5.4.1: 1 Summary of abnormal LFTs in Study 1160.26 (safety set)

LFT elevation	DE 110 bid N (%)	DE 150 bid N (%)	Warfarin N (%)
Total treated	5,984 (100.0)	6,059 (100.0)	5,999 (100.0)
ALT or AST > 1xULN and <= 2xULN	1,681 (28.1)	1,645 (27.1)	1,875 (31.3)
ALT or AST > 3xULN	121 (2.0)	111 (1.8)	126 (2.1)
ALT or AST > 5xULN	40 (0.7)	48 (0.8)	51 (0.9)
Bilirubin > 2xULN	126 (2.1)	116 (1.9)	127 (2.1)
ALT or AST > 3xULN + Bilirubin >2xULN	11 (0.2)	14 (0.2)	22 (0.4)

Subjects were counted in each category if the respective abnormal LFT event occurred between first dose of study medication and study termination visit.
Source: SCS Appendix 7, Table 3.1.1.2

Based on the 24 month mean duration of the trial, the rate of transaminase elevations >3x ULN is approximately 1% a year. This is similar to the rate seen with warfarin in the SPORTIF trials (Arora and Goldhaber, [P06-05618]). In comparison, ~7.6% of ximelegatran subjects had transaminase elevations >3x ULN.

Similarly, the relative risks of the LFT changes, when dabigatran and ximelagatran are compared with their respective control groups, are markedly different. For dabigatran versus warfarin, the relative risk for transaminase >3xULN is 1.00 and 0.91 and 0.52 and 0.66 for potential Hy's Law cases (Table 2.5.5.4.1: 2). For ximelagatran versus warfarin the corresponding frequencies are 7.6 % and 1.1% for transaminases >3xULN (relative risk 6.9) and 0.5% on ximelagatran and 0.05% and 0.06% on comparators for potential Hy's Law cases, a relative risk of 8.3 to 10 (the FDA calculated a relative risk of 6.6). In addition, 93% of transaminase elevations on ximelagatran occurred within 6 months of starting treatment, a different time course than observed for dabigatran or warfarin in RE-LY.

The calculations of relative risk of key measures of abnormal liver function were strong evidence for concluding that ximelagatran was associated with hepatotoxicity. In contrast, the relative risk assessments for dabigatran compared to warfarin show no such elevated risk.

Table 2.5.5.4.1: 2 Hazard Ratios and 95% CIs for LFT elevations in Study 1160.26 (safety set)

ALT/AST elevation	DE 110 bid vs Warfarin	DE 150 bid vs Warfarin	DE 110 bid vs DE 150 bid
ALT/AST>3xULN			
Hazard ratio (SE)	1.00 (0.13)	0.91 (0.12)	1.09 (0.14)
95% CI	0.78, 1.28	0.71, 1.18	0.85, 1.42
P-value	0.9820	0.4776	0.4955
ALT/AST>5xULN			
Hazard ratio (SE)	0.82 (0.17)	0.98 (0.20)	0.83 (0.18)
95% CI	0.54, 1.23	0.66, 1.45	0.55, 1.27
P-value	0.3363	0.9107	0.3991
ALT/AST>3xULN and total bilirubin >2xULN			
Hazard ratio (SE)	0.52 (0.19)	0.66 (0.23)	0.79 (0.32)
95% CI	0.25, 1.07	0.34 (1.29)	0.36, 1.74
P-value	0.0770	0.2252	0.5542

In case of recurrent event, the first event was considered
Source: SCS Appendix 7, Tables 3.1.1.5, 3.1.1.8 and 3.1.1.11

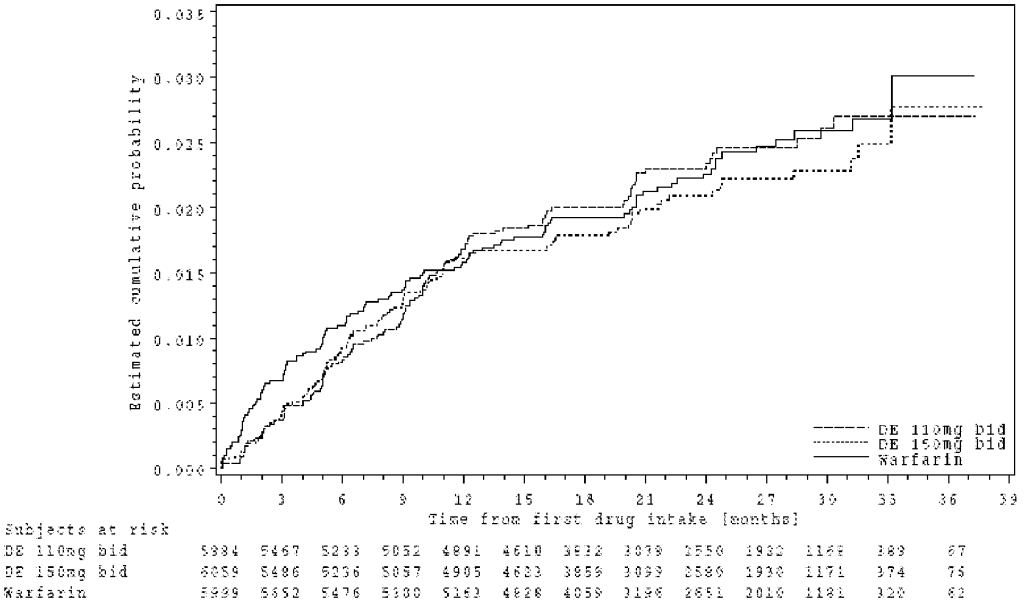


Figure 2.5.5.4.1: 1 Kaplan-Meier estimate of the first occurrence of ALT/AST >3xULN in study 1160.26 (safety set)

Source: SCS Appendix 7, Figure 3.1.1.7

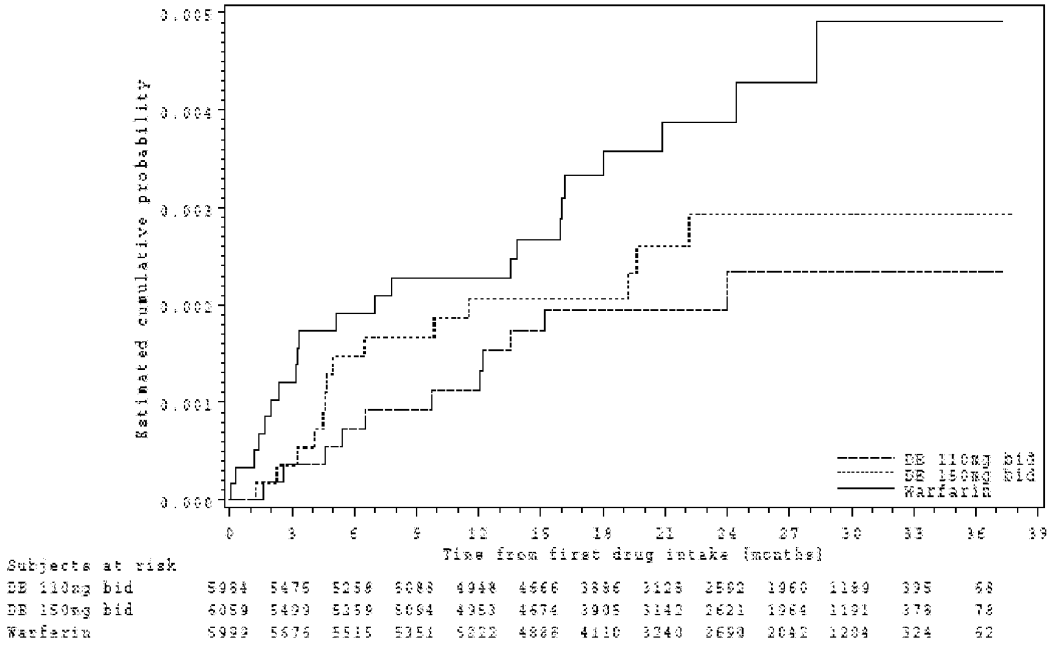


Figure 2.5.5.4.1: 2 Kaplan-Meier estimate of the first occurrence of abnormal LFT (ALT/AST >3xULN and total bilirubin >2xULN) in study 1160.26 (safety set)

Source: SCS Appendix 7, Figure 3.1.1.4

In summary, for all measures of hepatic abnormalities, the frequencies for dabigatran were the same or lower than those for warfarin. Transaminase elevations <2x ULN were 3-4% lower on dabigatran versus warfarin. For transaminase elevations >3x and >5x ULN, dabigatran rates were lower than warfarin. Most importantly, the frequency of potential Hy's Law cases was lower in the dabigatran groups than on warfarin. There were few (4) and equal numbers of these cases without a clear cause for the two substances. Therefore, based on all hepatic data collected and evaluated in RE-LY, we conclude that there is no evidence of any hepatic adverse effects of dabigatran.

2.5.5.4.2 Lab values, Blood Pressure and ECGs over time in RE-LY

Analyses of laboratory evaluations for the Phase II trials are included in the Summary of Clinical Safety. The results are consistent with the Phase III trial. The data is contained in the respective clinical trial reports (see [Module 5.3]).

Overall in Trial 1160.26, there were few clinically relevant changes from baseline to the end of treatment in mean hematology or chemistry measures in any treatment group.

Mean laboratory values

There were no clinically meaningful changes in mean laboratory values in this study. Mean values of AST, ALT, alkaline phosphatase, and bilirubin showed a slight decline at the end of treatment for all treatment groups (SCS Appendix 7, Table 3.2.1).

Mean hemoglobin values declined by 0.5 mg/dL at the end of treatment across all treatment groups, though the final mean values were within the normal range (14.3, 14.3, and 14.4 mg/dL for DE 110 bid, DE 150 bid, and warfarin, respectively). Mean decreases in hematocrit (1.3%, 2.7%, 1.2%), platelets (9, 8, 10 $x10^9$), and red blood cell counts (0.1, 0.1, 0.1 x 10^{12}) paralleled the decreases in hemoglobin. All mean values were within normal range at the end of treatment.

Individual subject shifts in laboratory values

There were no clinically meaningful treatment differences for shifts in laboratory values. An evaluation of subjects who shifted from a normal (or low or high) laboratory value at baseline to a low or high (or normal) value at the end of treatment is summarized in the RE-LY clinical trial report, 1160.26 [U09-3249-01] Table 15.3.3.2: 2. Subjects with changes in laboratory values that would be considered of possible clinical relevance are discussed below.

The number of subjects with laboratory values outside the normal range at end of treatment was generally low for most laboratory measures (based on the percent of subjects with normal values at baseline). Concordant with the observations above on mean changes in hematology, there were shifts to low values of hemoglobin and hematocrit. DE 150 caused a greater number of shifts than DE 110 or warfarin. For hemoglobin, 7.8%, 8.9%, and 7.6% for DE 110 bid, DE 150 bid, and warfarin subjects, respectively had shifts to below the lower limit of normal. A greater number of warfarin subjects shifted from normal to low values in platelet counts at the end of treatment compared with dabigatran (3.6%, 3.4%, and 4.4%) [U09-3249-01] Table 15.3.3.2: 2.

Commensurate with chages in mean values of liver function tests, warfarin was associated with a higher proportion of shifts to above the ULN.

Clinically Relevant Changes in Laboratory Values

Shifts outside the normal range were further characterized by clinical relevance based on pre-defined laboratory guidelines (1160.26 [U09-3249-01] Appendix 16.2.8, Listing 1.3).

Based on the pre-defined guidelines, a greater percentage of DE 150 bid subjects had clinically relevant changes in hemoglobin and hematocrit (hemoglobin: 7.7%, 8.4%, and 7.4% of DE 110 bid, DE 150 bid, and warfarin subjects, respectively; hematocrit: 4.2%, 4.5%, and 3.8%). Potentially clinically relevant decreases in platelet count occurred in 0.1% of subjects across all treatment groups (SCS Appendix 7, Table 3.2.2).

Blood Pressure

In Trial 1160.26, the mean change from baseline in sitting systolic and diastolic blood pressure was determined monthly by treatment (SCS Appendix 7, Table 4.1.1). Mean systolic and diastolic blood pressure results were generally 1 to 2 mmHg lower than baseline throughout the trial, with no clinically meaningful differences between treatment groups.

Electrocardiograms and heart rate

As expected, the majority of subjects (73.9%) had an arrhythmia of AF at baseline based on 12-lead electrocardiogram (ECG); 20.1% of subjects had a normal sinus rhythm at baseline and 2.6% of subjects had pacemakers (atrial, ventricular, or both). There was a slight shift in the percentage of subjects with AF at the end of treatment (67.5%), as well as those with a normal sinus rhythm (22.4%). The percentage of subjects undergoing cardioversion therapy (electrical or pharmacologic) was modest during the study (approximately 7%), and was similar across treatment groups.

The mean heart rate (ventricular) was similar across treatment groups at baseline (76 bpm) and generally remained stable throughout the study. ECG is summarized in the clinical trial report (1160.26 [U09-3249-01] Tables 15.3.4: 1-5).

2.5.5.5 SAFETY CONCLUSIONS

- For the primary safety endpoint of major bleeding, DE 110 treatment resulted in 21% lower risk of major bleeding events compared with warfarin treatment (p=0.0021). DE 150 had similar risk of major bleeding compared with warfarin (7% decrease, p=0.322)

- DE 110 treatment resulted in 15% lower risk of major bleeds compared with DE 150 (p=0.0356)

- Both doses of dabigatran reduced the rate of life-threatening bleeds compared to warfarin, 33% (p=0.0003) and 18% (p=0.047) for DE 110 and DE 150, respectively

- Hemorrhagic stroke risk decreased 69% for DE 110 compared to warfarin (p=0.0001) and 74% for DE 150 compared to warfarin (p<0.0001)

- Intracranial hemorrhage risk decreased 71% for DE 110 compared to warfarin (p<0.0001) and 59% for DE 150 compared to warfarin (p<0.0001)

- Both doses of dabigatran resulted in a relative risk reduction in all bleeding (major +minor) compared to warfarin. For DE 110, the risk reduction was 21% (p<0.0001) and for DE 150 the risk was reduced 9% vs warfarin (p= 0.0029). The lower dabigatran dose led to significantly less bleeding (14%) than the higher dabigatran dose (p< 0.0001).

- Subjects treated with DE 150 had a higher incidence of major bleeding events within the gastrointestinal tract when compared with warfarin (1.5% per year versus 1.0% per year, p=0.0004).

- There was a significant interaction between treatment and age for the rate of major bleeds. In subjects ≥ 75 years, the relative risk of major bleeding for DE 150 vs warfarin was in favor of warfarin. For ICH and hemorrhagic stroke, the benefits of dabigatran versus warfarin in this subgroup still persisted.

- The use of ASA nearly doubled the risk of major bleeds across all treatment groups but did not change the relative risks. There were no concurrent medications that differentially increased major bleeds across treatment groups.

- In general, previous VKA exposure did not appear to increase major bleed rates across all treatment groups.

- Within GI AEs, the constellation of dyspepsia/stomach discomfort/gastritis was twice as frequent for dabigatran as for warfarin, with no difference between dabigatran doses.

- Nausea and diarrhea were more frequent for dabigatran compared to warfarin.

- AEs leading to discontinuation were more 4-5% frequent in the dabigatran groups compared to warfarin (19% for DE 110, 20.5% for D150, and 15.6% for warfarin).

2.5.5.6 DATA RECEIVED AFTER DATABASE LOCK

After database lock the data coordinating center, PHRI, continued to query the sites for the outcome events that had not been clarified. They received documentation of 6 major bleeds (of which 4 were ICH events), 2 ischemic strokes and 2 deaths. Corrections to the date of one myocardial infarction and to cause of death for two cases also were collected. (see [Module 1.11.3] for the list of events post-DBL). When the efficacy and safety endpoints were analysed including this data, there were minor changes. The deaths were both in the DE150 bid treatment group and this changed the p-value on all cause mortality from 0.047 to 0.052. The bleed data did not change any of the main conclusions but the difference in major bleeding between DE 150 bid and DE 110 bid was no longer significant (p=0.05). The additional analyses including these data are provided in [SCE Appendix 6, Tables and Figures 2.1.1.7.1 – 10 and SCS Appendix 7, Tables 2.1.1.1.5: 1 and 2].

In the process of site closeouts, which included source documentation verification, additional events were identified in the source records. These will be summarised and submitted.

2.5.6 BENEFITS AND RISKS CONCLUSIONS

Benefits

Dabigatran etexilate, either 110 or 150 mg twice daily, is effective in the prevention of stroke and systemic embolism in subjects with AF and at least one risk factor for stroke. At a dose of 150 mg twice daily, dabigatran is more effective than warfarin in prevention of stroke, systemic embolism and vascular death. At a dose of 110 mg twice daily, dabigatran is as effective as warfarin in the prevention of stroke systemic embolism and death.

The stroke rates for DE 110, DE 150 and warfarin were 1.10%/year, 1.53%/year and 1.69%/year respectively. The relative risk reductions for stroke and SEE compared to warfarin were 9% and 36% for DE 110 and DE 150, respectively. In addition, ischemic stroke was reduced by 24% for DE 150 compared to warfarin.

The risk of death (all cause and vascular) was lower for both doses of dabigatran compared with warfarin. All cause mortality was reduced by 12% for DE 150 compared to warfarin. Most of this effect was due to a reduction in vascular death (15%, p=0.0425). All composite endpoints which included all cause death or vascular death showed a benefit of dabigatran compared to warfarin, ranging from 3% to 17% with the DE 150 dose usually showing the greater effect.

Both doses of dabigatran significantly reduced the occurrence of hemorrhagic stroke compared to warfarin ($p<0.0001$). The relative risk reductions were 69% and 74% for DE 110 and DE 150 compared to warfarin.

Intracranial hemorrhage decreased 71% for DE 110 compared to warfarin ($p<0.0001$) and 59% for DE 150 compared to warfarin ($p<0.0001$).

The absolute risk of myocardial infarction was low (0.5 to 0.7%/year) but was greater on dabigatran (relative risks 1.35 and 1.38, p=0.07 and 0.049 for DE110 and DE 150 compared to warfarin).

Net clinical benefit, using several different combinations of endpoints, all substantiate the benefit of dabigatran compared to warfarin.

Risks

The principal risk of anticoagulation is bleeding. The major bleeding rates for dabigatran, DE110 and DE150, were 2.67%/year and 3.11%/year, compared to warfarin with 3.36%/year. Relative to warfarin, the major bleed rates were reduced by 21% for DE 110 and 7% for DE 150. The lower dose of dabigatran had significantly lower (15%) major bleed rates than the high dose of dabigatran.

A sub-category of major bleeds, life-threatening bleeds, was significantly less frequent with dabigatran treatment. Compared to warfarin, both doses of dabigatran reduced the rate of life-threatening bleeds, 33% and 18% for DE 110 and DE 150, respectively. In terms of morbidity and mortality, the clinically most important elements of life-threatening bleeding are

intracerebral hemorrhage (hemorrhagic stroke) and intracranial hemorrhage. The benefit of dabigatran over warfarin in lowering the frequency of these events was listed under benefits.

Both doses of dabigatran resulted in a reduction in any bleeding (major +minor) compared to warfarin. For DE110, the relative reduction was 21% and for DE150 it was reduced 9% The lower dabigatran dose led to significantly less bleeding (14%) than the higher dabigatran dose.

Gastrointestinal bleeding was also more frequent on dabigatran, notably major GI bleeding with the DE150 dose compared to warfarin (1.5% vs. 1%).

In subjects with life-threatening bleeding, dialysis should be considered. Dialysis is effective in removing dabigatran from the circulation. Based on preclinical data and limited clinical experience the use of prothrombin complex or recombinant Factor VIIa to counteract life-threatening bleeding can also be considered

Dyspepsia and related symptoms were twice as frequent on dabigatran as warfarin (15% vs. 7%) but this seldom was a serious adverse event and led to discontinuation of treatment in approximately 2% of subjects compared to 1% on warfarin.

Sub-populations

The effectiveness of dabigatran in stroke prevention is remarkably consistent over a wide range of patient subgroups expected to receive the drug. The most important subgroups were those classified by renal function, age, gender, and $CHADS_2$ risk score. In post hoc analyses of a subgroup of subjects well controlled on warfarin, the benefits of dabigatran compared to warfarin persist. Only the reduction in vascular death compared to warfarin appeared to be limited to subjects who were not well-controlled on warfarin.

In assessment of bleeding risks across sub-populations, for subjects $\geq$ 75 years, the bleeding risk of DE150 approached or exceeded that for warfarin. However, the efficacy in this subgroup was also higher with DE 150. There may be individual patients where the bleeding risk outweighs the stroke risk. In such cases, a dose of DE110 may be preferred. A dose of DE110 may provide a wider safety margin.

For the risk of stroke or major bleeding as determined by $CHADS_2$ risk scores, the benefit/risk for dabigatran is favorable. For $CHADS_2$ scores $\geq$ 3, which is frequently indicative of an elderly subject, bleeding rates are slightly higher than for warfarin but with increased efficacy. There may be individual patients where the bleeding risk outweighs the stroke risk. In such cases, a dose of DE110 may be preferred. A dose of DE110 may provide a wider safety margin.

Subjects with moderate renal dysfunction (30-50 mL/min CrCl) have an increased risk of bleeding with both warfarin and dabigatran compared to subjects with no renal dysfunction. In this sub-population, the major bleeding rates on either dose of dabigatran are less than the rates on warfarin.

None of gender, weight, or ethnic origin (Asian versus Caucasian) had any relevant effects on the bleeding or efficacy with dabigatran.

There may be subjects who have multiple risk factors for increased bleeding risk that together may substantially increase risk. Concomitant antiplatelet use, concomitant P-gp inhibitor use, age ≥ 75 years, moderate renal dysfunction, previous GI bleeding, high $CHADS_2$ scores (≥ 3), are all factors that may increase bleeding risk. While there may also be increased benefit in such subjects, the risk of bleeding may potentially outweigh the risk of stroke and a dose of 110 mg bid may be considered.

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test maybe useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec is associated with a higher risk of bleeding.

Drug Interactions

Dabigatran is not metabolized by the cytochrome P450 system. No interactions have been detected nor are any expected. P-glycoprotein inhibitors (e.g. verapamil, amiodarone, quinidine, ketoconazole, clarithromycin) increase the absorption of dabigatran etexilate up to 2.8-fold in Phase I studies. In RE-LY, the increased plasma concentrations in subjects taking amiodarone and verapamil were modest, up to 20%, and no increases in bleeding rates could be detected. Nevertheless, caution is advised when these drugs are used concomitantly with dabigatran. For ketoconazole, no Phase III data was available and the increased plasma levels from Phase I support contraindicating systemic ketoconazole. In Phase I studies drugs that decrease gastric acidity (proton pump inhibitors, H2-blockers) decrease the absorption of dabigatran up to 25%. Minimal concentration changes and no effect on bleeding was seen in the RE-LY trial. There is no restriction on the use of these drugs. Antiplatelet drugs (ASA, clopidogrel, ASA+clopidogrel, NSAIDs) increased the risk of bleeding in subjects taking dabigatran or warfarin. For concomitant use of ASA or clopidogrel or the combination, the risk of bleeding was approximately doubled; for NSAIDs the bleeding risk increased by ~50%. Caution is advised when these drugs are co-administered with dabigatran.

Conclusions

Based on data presented in this document, the recommended dosage of dabigatran etexilate is 150 mg taken orally, twice daily for the reduction of stroke, SEE and vascular mortality compared to warfarin. For patients in whom the risk of bleeding may be increased, a dose of 110 mg taken orally, twice daily may be considered (see SCS, Module 2.7.4).

The doses of dabigatran etexilate tested in RE-LY, DE 110 and DE 150, were demonstrated to be non-inferior but also have major benefits compared to warfarin. Dabigatran does not need to be monitored and no dose adjustment is required. There are no food interactions and there are few relevant drug interactions. Both doses reduce the risk of stroke/SEE as well or better than warfarin. Both doses profoundly reduce the risk of hemorrhagic stroke and intracranial bleeding compared to warfarin and both doses decrease vascular mortality, with the benefit of the high dose statistically significant. The high dose, DE 150, decreases the rate

of ischemic stroke, hemorrhagic stroke, intracranial bleeding, life-threatening bleeding, vascular mortality and any bleeding compared to warfarin. The low dose, DE 110, decreases major bleeding, hemorrhagic stroke, intracranial bleeding, life-threatening bleeding, and any bleeding compared to warfarin but is not as effective as DE 150 in prevention of ischemic stroke and vascular mortality. DE 110 decreases major bleeding and any bleeding more than DE 150. For dabigatran, the risk of gastrointestinal bleeding is increased, especially with the high dose. The incidence of MI is higher than for warfarin but is not dose-dependent. There is an incidence of ~12-13% of subjects with dyspepsia/abdominal discomfort compared to ~6% on warfarin. These risks are more than counterbalanced by the benefits seen with both doses on multiple measures of morbidity and mortality in AF patients.

The benefit/risk assessment based on the demonstrated non-inferiority or superiority of dabigatran versus INR-adjusted warfarin for stroke prevention, together with the reduced frequency of major and minor bleeding is consistent across a wide range of subgroups and demographic characteristics and highly clinically significant.

Atrial fibrillation is a leading cause of ischemic stroke. Stroke in a patient with atrial fibrillation is associated with greater mortality, morbidity and costlier hospital stays than in stroke patients without AF. While warfarin and other vitamin K antagonists have been shown to be effective, they have a narrow therapeutic window necessitating regular monitoring to achieve the target therapeutic range of 2.0-3.0, where warfarin treatment has been shown to offer an acceptable benefit/risk ratio.This is further complicated by many drug-drug and numerous drug-food interactions. The monitoring is is inconvenient for patients and negatively affects compliance and discontinuation rates. A significant proportion of patients fails to achieve stability within the target range. This suboptimal anticoagulation is associated with poor outcomes either in terms of thrombotic events, hemorrhages or mortality. Due to the limitations of warfarin and other vitamin K antagonists they are still under-prescribed in patients with AF, particularly the elderly, those patients who have the highest risk of stroke.

The large and consistent reduction in hemorrhagic stroke and intracranial hemorrhage, catastrophic adverse outcomes of anticoagulation therapy, with both doses of dabigatran etexilate represent a milestone advance in the prevention of stroke in AF. The fear of these bleeding events is a major factor in the under-use of anticoagulation in moderate to high risk patients with AF. In addition, the high dose of dabigatran decreases the risk of ischemic stroke compared to warfarin. Based on these conclusions, the data in this application demonstrate that both DE 150 and DE 110 both have significant advantages compared to warfarin with acceptable risks and strongly support registration of dabigatran etexilate for the reduction of stroke/SEE and vascular mortality.

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